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CLEFT PALATE

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IN 1925, Dorrance proposed the so-called "push-back" operation. This operation was devised to obtain complete velopharyngeal closure—a condition essential in any cleft palate operation to assure a normal voice control. In 1927, he emphasized the fact that early cleft palate operations, *i.e.*, before the fourth year, frequently failed in whole or in part. We have frequently stated that patients upon whom three or four operations were necessary to obtain closure of the cleft palate have hard, fibrous, inflexible palates. This invariably leads to poor phonation.

We felt at that time (1927) that there were quite a few cases where the palate could not be brought back to the posterior wall of the pharynx. With passing years, this group has been greatly reduced.

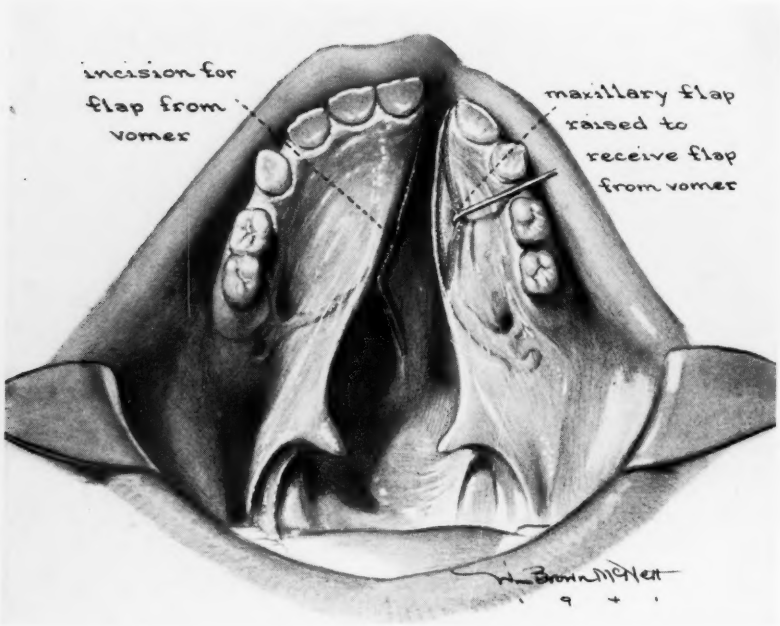
While we are sure that the "push-back" operation overcame one of the chief faults of the standard cleft palate operations, *viz.*, a short palate, we were keenly aware that perfection had not been obtained. The hole left in an anterior palate in complete clefts or in unilateral lip-jaw splits, even when a good fitting plate was used, was an affront to the surgical mind.

Progress was made, from time to time, by varying procedures—some of them previously proposed by other surgeons and others devised or modified by us to conform with problems occurring in the "push-back" operation. We are reporting on two distinct additional procedures, both of which, during the past five years, have given very satisfactory results.

The first of these is the use of the mucoperiosteum of the vomer. We find that Lannelongue, in 1872, was the first to utilize a portion of the vomerine mucoperiosteum to close off the nose from the oral cavity. He dissected the mucoperiosteum, leaf-like, from one side of the vomer, and sutured the free end under the palatal mucoperiosteum. Veau sutures the vomerine flap to the nasal mucous membrane and covers part of the mucous membrane with a palatal flap. In the light of our experience, we find it is much easier, and surer, to obtain raw surface-to-raw surface by suturing the vomer flap under the palatal tissue (Figs. 1, 2, 3 and 4). We see no advantage in adding a palatal flap, as it complicates later operations.

The value of vomer flap procedure in "push-back" operations was ob-

FIG. 1.



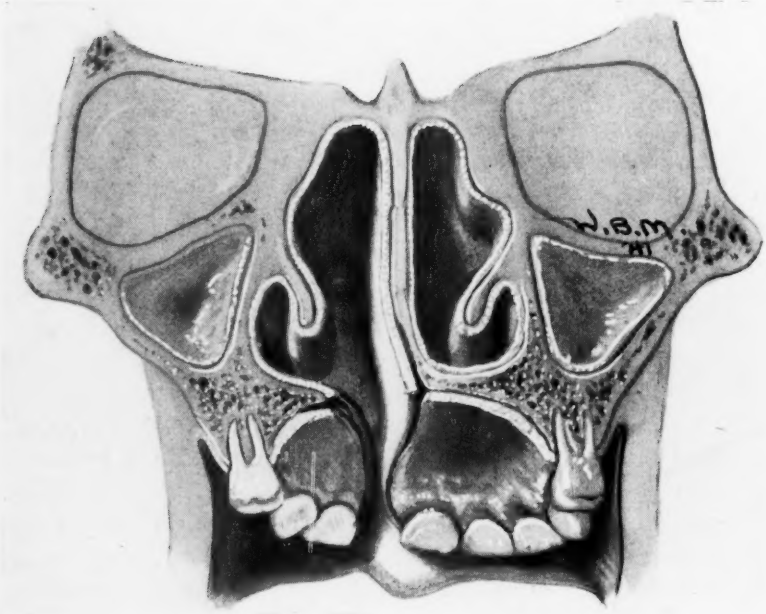


FIG. 2.

FIG. 1.—Incision for the vomer flap.

FIG. 2.—Transverse view of the incision and elevation of the flaps from the vomer.

FIG. 3.

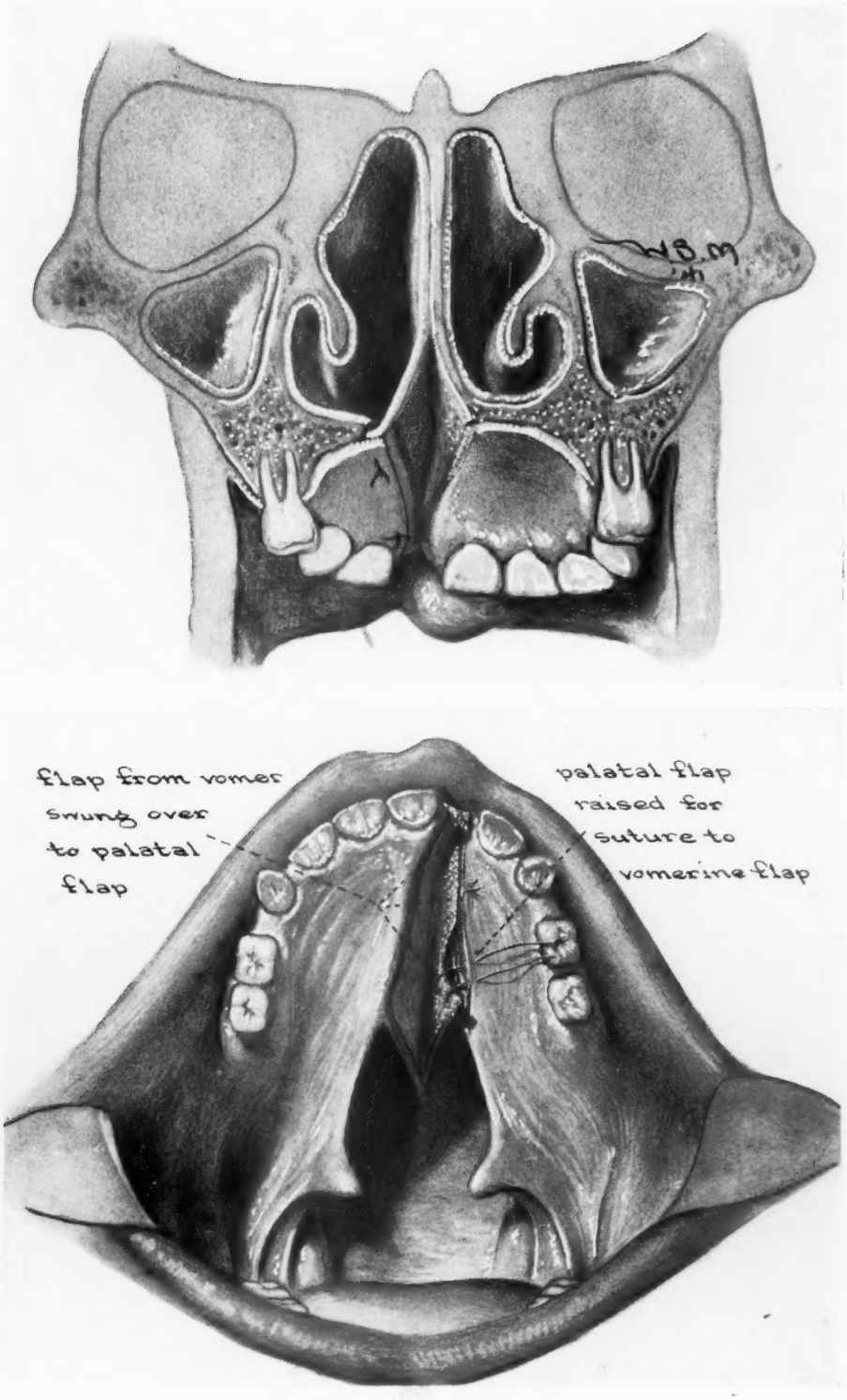
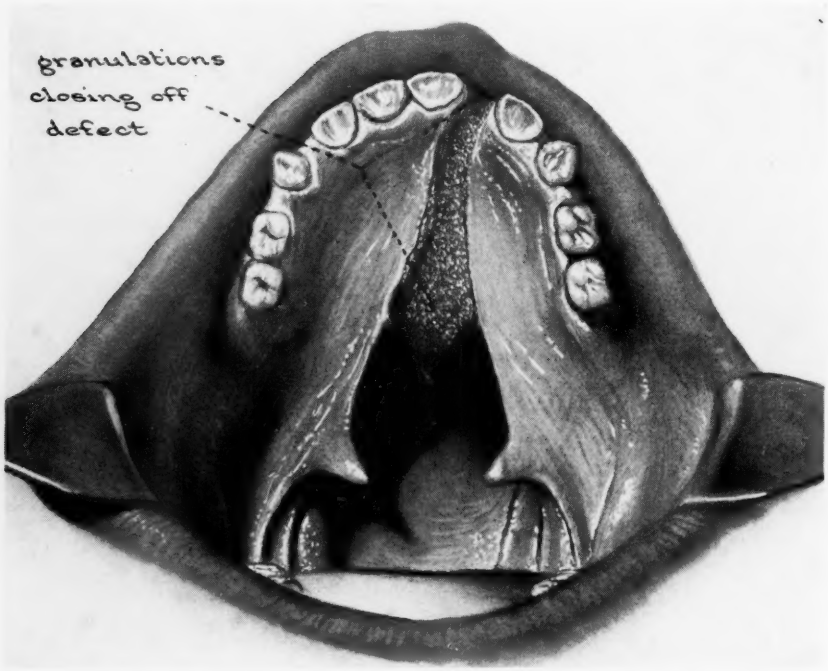


FIG. 4.

FIG. 3.—Transverse view of the completed vomer flap.

FIG. 4.—Suturing of the flap in the vomer transplantations.

FIG. 5



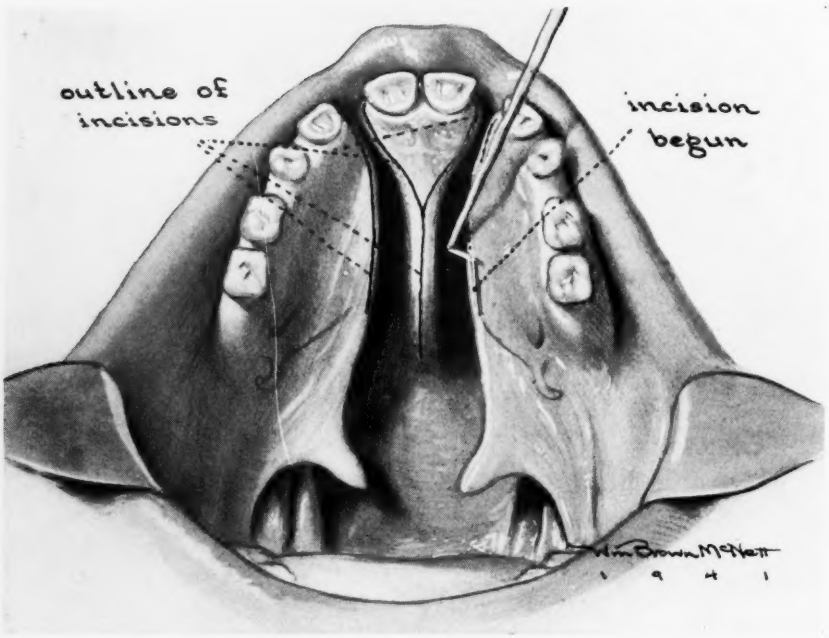


FIG. 6.

FIG. 5.—Completed and filled in vomer-flap operation in single lip-jaw palate cleft.

FIG. 6.—Lines of incision for bilateral vomer flaps in a double lip-jaw palate cleft. Note how far forward they may be placed.

vious and if, in addition, we could fill up the cavity formed with granulation tissue, we would greatly enhance the operation. This was achieved by packing the area with iodoform gauze, and holding it in place, as shown in Figure 10. In double, complete cleft palate, Pickler advised the double vomerine flap. We have used this, extending the flaps further anteriorly. We have had no failures in obtaining a granulating surface, which usually fills in flush with the palatine bones (Figs. 2 to 10 inclusive).

The second addition to the original "push-back" operation is the lining of the palatal mucoperiosteum flap with a Thiersch or split-skin graft: A split- or Thiersch skin graft is sutured in place under each flap raw surface-to-raw surface (Figs. 17, 18, 20, 23, and 28). Since adopting this procedure, crust formation has been diminished. The contracture of flaps when finally displaced backward in the second stage is either completely eliminated or greatly minimized. In order to assure a take, pressure on the flap is necessary. This is accomplished by placing iodoform gauze over the flaps. The gauze is maintained at a constant fixed pressure by strands of silver wire inserted between the posterior teeth and then carried across the palate to pass between the last two teeth on the opposite jaw; the ends are then carried across the mucous membrane above the incisor teeth; the ends of the wire are twisted together and bent back across the palate, being held in place under the horizontal wire which passes between the posterior teeth (Fig. 10). In our last 10 cases we have substituted a splint designed for us by Dr. P. Gross. It is described in the American Journal of Orthodontia and Oral Surgery, September, 1942. The wire and gauze are removed in 10 to 12 days.

While each cleft palate requires special modifications of technic, one can outline specific procedures which will be applicable to each type commonly met with:

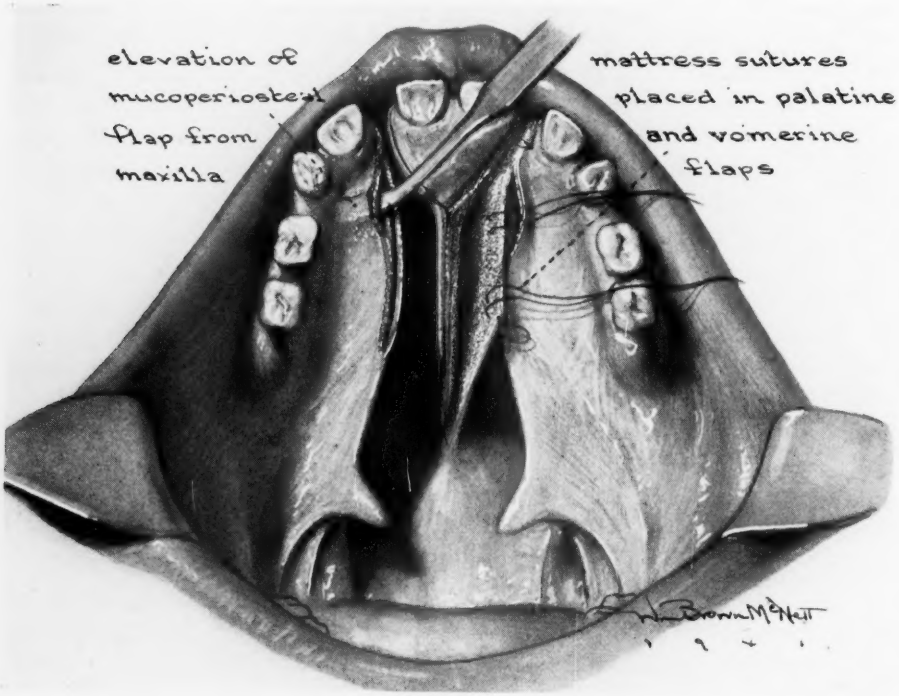
TYPE I—CONGENITAL SUBMUCOSAL OR CONGENITAL INSUFFICIENCY OF THE PALATE AND CLEFT OF THE SOFT PALATE

The shortening in these types of cleft palate is almost invariably due to a deficiency of the horizontal plate of the palate bone (Fig. 11). Since the soft palate is attached by the palatine aponeurosis to the shortened horizontal plate, the shortening is in direct proportion to the bony deficiency. Obviously, the simple repair of any cleft in the soft palate cannot have the slightest effect in accomplishing velopharyngeal closure.

We advise, and routinely carry out, the following procedures: (1) We attempt to find the amount of bone deficiency by the insertion of a needle at various points, as shown in Figures 12, 13 and 14. (2) In all cases, we perform the two-stage "push-back" operation.

FIRST STAGE OF THE "PUSH-BACK" OPERATION

The first stage consists of raising the flap by Method A, Fig. 15, or B, Fig. 19. Method A is selected if we are dealing with a fairly normal, well-developed flap with adequate blood supply. In these cases, the palatine vessels



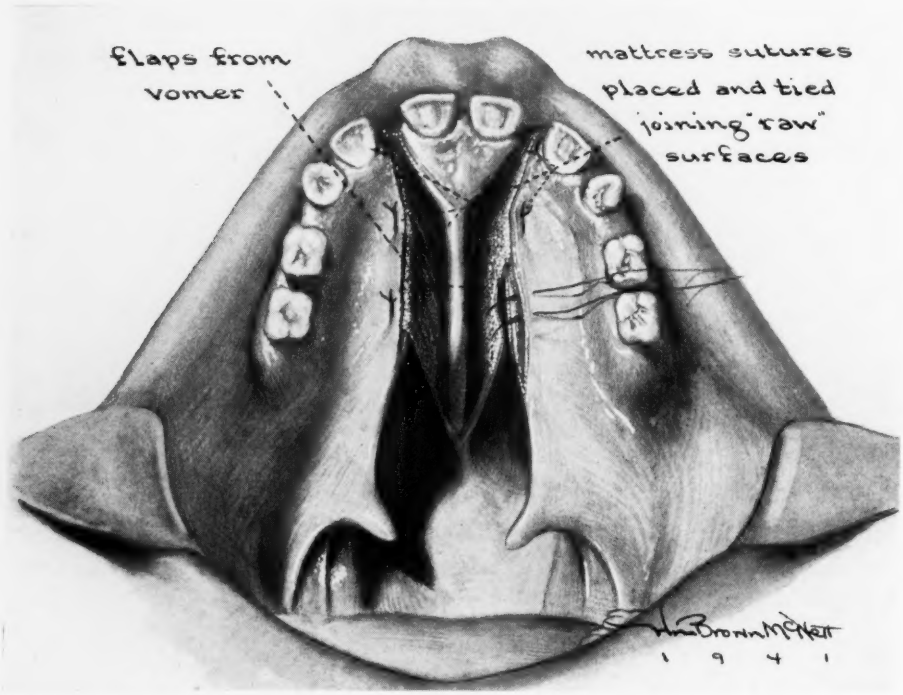


FIG. 7.—Demonstrating the method of elevating and suturing the vomer flap in double lip-jaw palate cleft.

FIG. 8.—Completed double vomer flap in double lip-jaw palate cleft.

are divided (an absolute necessity to obtain sufficient backward displacement). When the flap is raised, a skin graft is sutured in place on the palatine mucoperiosteum, as shown in Figures 16, 17, and 18. The flaps are returned to their bed and the edges sutured. In some cases where the palatine mucosa is thin, or where a considerable bony defect is present, or where the blood supply does not appear to be adequate, Method B is employed (Fig. 19). In those cases, the palate is raised, leaving a bridge of undivided tissue to insure blood supply. The remaining portion of the flap is freed completely from the bone and the palatine arteries are divided, as in Method A. The flaps are then sutured back in their normal position.

We have noted that the flaps thicken appreciably following this procedure. If, when the second stage is being performed, we find the flaps

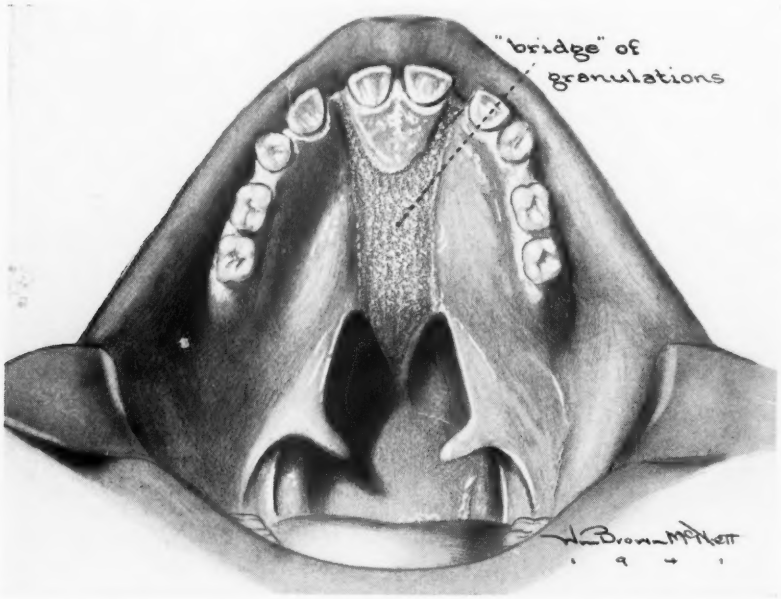


FIG. 9.—Final results of the vomer flap in bilateral lip-jaw palate cleft.

are not of sufficient thickness, we raise them and again replace them and wait for another four or ten weeks before elevating and placing the skin grafts, after the method outlined above.

We deliberately avoid using the nasal mucous membrane, because in performing the second stage of the "push-back" operation it is necessary to divide the nasal mucous membrane and aponeurosis at its attachment to the bone, thus leaving a raw area. If the nasal mucous membrane is not divided, complete velopharyngeal closure will not be obtained in many cases because the muscles responsible for this closure will not be restored to their normal position.

SECOND STAGE OF THE "PUSH-BACK" OPERATION

A flap is raised through the former incision, the nasal mucous membrane

being divided from the posterior bony palate (Fig. 20). The hamular process is then divided, thus transposing the tensor palati muscle from a tensor to an elevator muscle. The incision is continued around the tuberosity of the maxilla and over the pterygomandibular fold, freeing the palate from all bony attachments.

The uvula now rests on the posterior pharyngeal wall. The anterior portion of the flap is sutured to the fibrous membrane at the apex of the defect, and is also immobilized by passing one or two aluminum-bronze wires first through the bony palate, then through the apex of the flap on either side of the midline. Each wire is then twisted until the flap is held securely; the ends of the wire are then bent back, thus preventing any injury to the flap and tongue (Fig. 21).

The bony palate and lateral sulci, now devoid of their covering as a result of the push-back operation, are covered and packed with iodoform

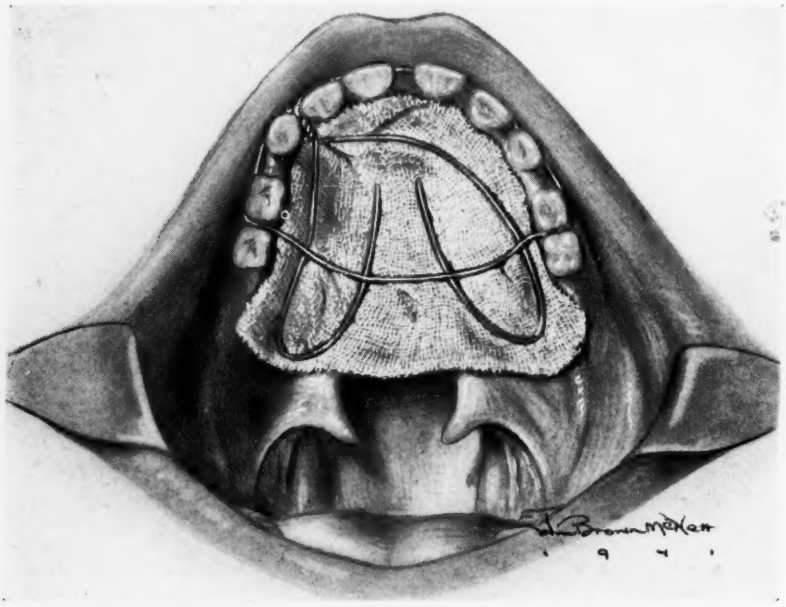


FIG. 10.—Method of placing silver wire to hold the iodoform gauze in place.

gauze, which is held in place by a strand of silver wire inserted as previously described (Fig. 10). The gauze is allowed to remain in place 10 to 14 days.

A summary of the necessary steps involved in the correction of congenital insufficiency of the palate follows:

Method A.—1. Raise the flap and suture the skin graft in place. 2. Three to ten weeks later, perform the "push-back" operation. Method B.—1. When the viability of the palatal tissue is uncertain, a three-stage operation should be performed. First raise the palatal flap, divide the palatine vessels, and suture the flap back in place. 2. Six to eight months later, raise the flap through the original incision and insert the skin graft. 3. Three to ten weeks later, complete the repair with the "push-back" operation.

TYPE II—CLEFT OF THE SOFT PALATE

This group of defects presents not only a short or insufficient palate but, in addition, a cleft of the soft palate (Fig. 12). The operation of choice in these cases is the two-stage "push-back" operation (Fig. 16).

The second stage of the "push-back" operation is now accomplished by raising the flap, dividing the hamular process on either side, severing the connections of the soft palate from the nasal surface of the bony palate. In this way, the nasal mucous membrane and the aponeurosis are separated from the posterior border of the hard palate (Fig. 20).

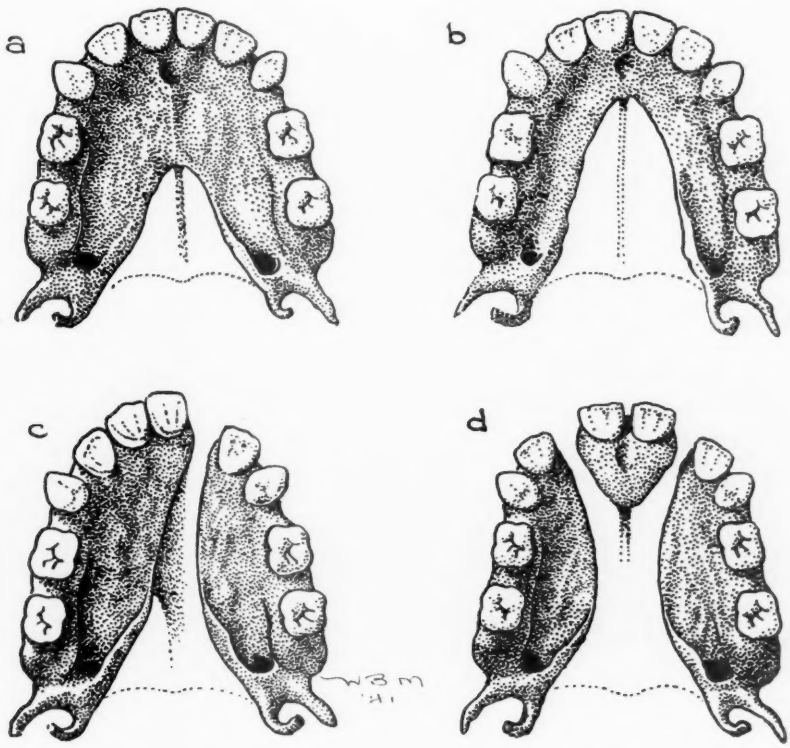


FIG. 11.—Deficiency of the bone in different variations of cleft palate.

The next step is to denude the edges of the cleft and approximate the nasal muscous membrane of the two halves, with interrupted sutures (left untied) (Fig. 21). It will be found helpful to insert a few mattress sutures to evert the edges and prevent inversion of edges—a frequent cause for nonunion. One or two Veau sutures are next placed through the muscular layer at the middle third of the soft palate. We use a specially designed needle for placing this intramuscular suture, bringing it from the midline out through the lateral incisions, as shown in Figures 21 and 22, and ending in midline. These needles—straight or curved—with wire sutures attached, are prepared for us by the Davis and Geck Co. The suture is placed and left untied; the nasal sutures are tied, closing this surface, with the edges everted.

The Veau suture is now twisted (tied) bringing the two halves of the cleft into good approximation, without tension. The oral sutures are next inserted and tied. These sutures should pass down to, but not through the nasal mucosa. Ordinary through-and-through sutures, if not carefully laid and tied, will invert the edges of the mucous membrane. Use end-on-end mattress sutures. The anterior end of the flap is now sutured to the palate bone or to the fibrous tissue present. An iodoform pack is placed over the uncovered palate and in the lateral incisions (Fig. 10).

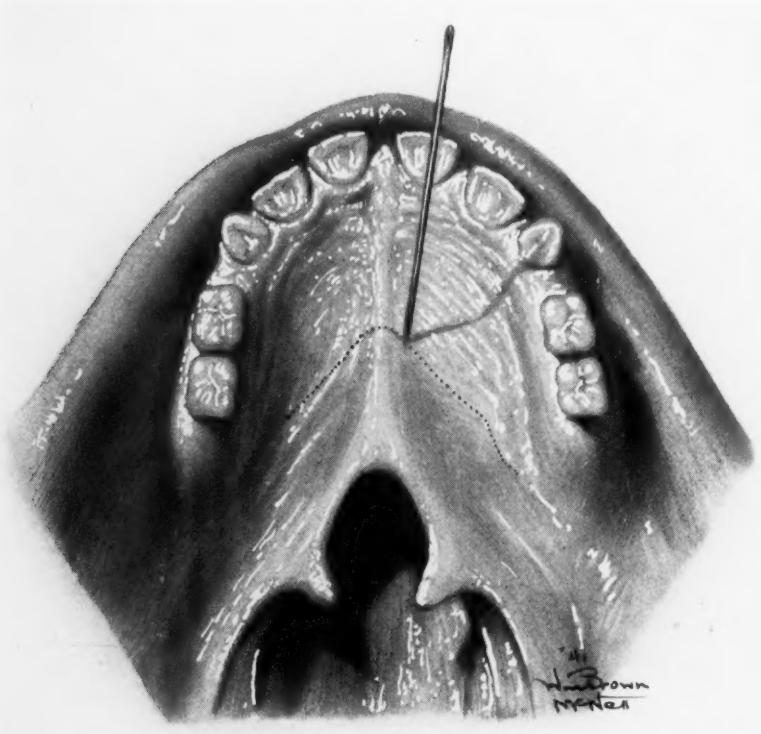


FIG. 12.—Determining the bone deficiency.

The raw nasal surface that formerly existed in the "push-back" operation is avoided by the use of the skin graft (Fig. 23). Tension sutures, or metal plates, used to reduce tension will frequently produce a permanent scar. Intramuscular and intrafascial sutures are well tolerated and, for this reason, the Veau suture is ideal. We use it in all cases. The mattress suture is well tolerated because it gives maximum approximation of the two muscular segments with epithelial or surface tissue compression.

A summary of the operative procedure in this type is: 1. Raise the flap and suture a skin graft in place. 2. Three to ten weeks later, the "push-back" is completed.

If the palatal tissues do not warrant extensive surgery at this time, a three-stage procedure should be employed:

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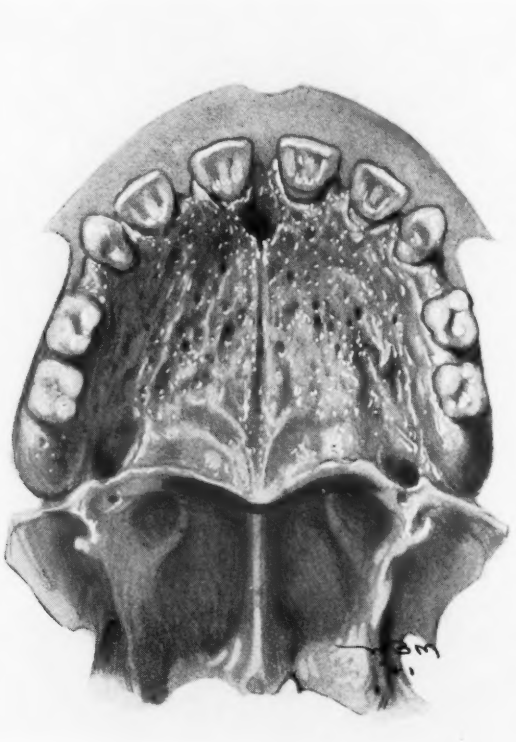


FIG. 13.—Normal bones in the palate. (Red border indicating where the palatine aponeurosis should be attached).

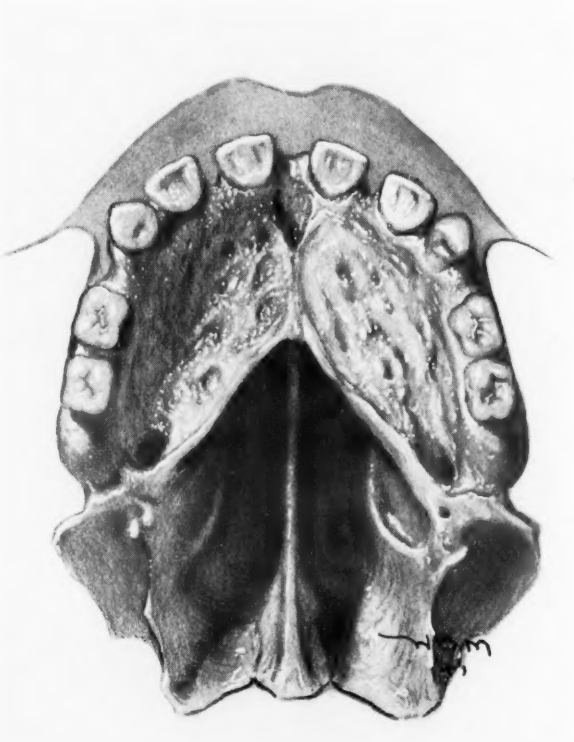
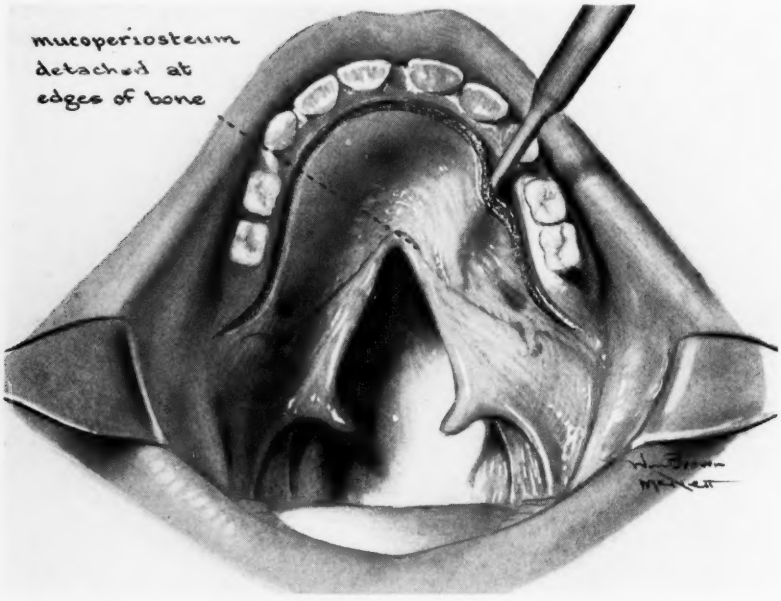


FIG. 14.—Note the loss of bone in a submucous or cleft of the soft palate. (Rough area is where aponeurosis would be retracted to, thus shortening the palate).

FIG. 15.



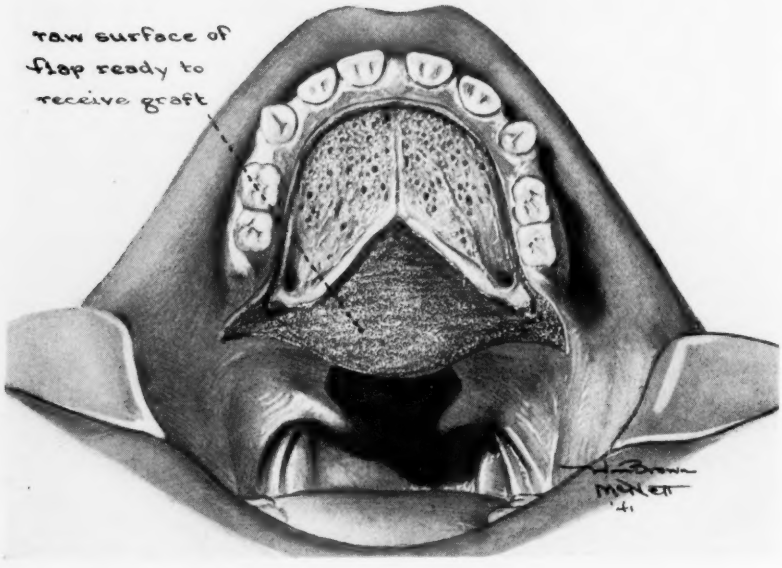


FIG. 16.

FIG. 15.—Method A—For elevation of the mucoperiosteal flap.

FIG. 16.—Flap elevated—Vessels divided ready for skin graft.

FIRST STAGE: Raise the flap, sever the palatine vessels and suture back in place.

SECOND STAGE: Six to eight months later, raise the flap through the original incision and insert the skin graft—resuture.

THIRD STAGE: Three to ten weeks later, perform the "push-back" operation.

TYPE III—CLEFT OF THE SOFT AND HARD PALATE UP TO THE PREMAXILLA

This group presents four distinct variations: 1. The defect in the palate bone may be as wide as the cleft in the soft palate. 2. The margins of the soft palate cleft may converge anteriorly into the narrow cleft of a very poorly developed hard palate, with its characteristically high narrow arch. 3. The vomer may be fairly well developed or only rudimentary.

In our experience, the vomer is usually rudimentary and does not approach the level of the defect. These variations affect the type of operative procedure. The presence or absence of a normal vomer is the most important factor present. When the vomer is rudimentary, as is usual in this type of cleft, it plays no part in the correction. The Langenbeck lateral incision may be made, the flaps raised and the skin grafted in one operation. Three weeks later, the Langenbeck operation is performed closing the cleft. Six months later, the V-"push-back" operation is performed.

The Wardill operation uses the Veau-method of stretching the mucous membrane and covering it with V-flaps, much the same as we do in the V-"push-back." If the vomer is well developed, we perform the "push-back" as described in Type V.

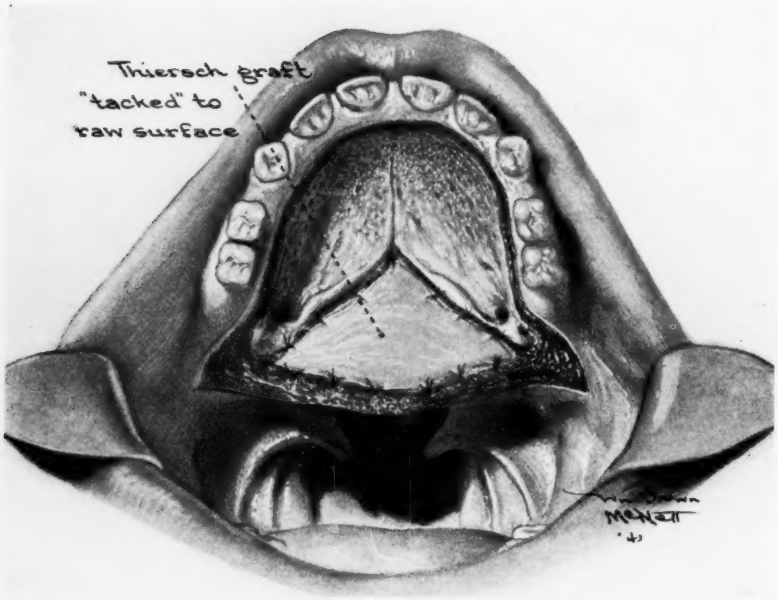
The practicability of the Veau idea of reflecting the nasal mucous membrane must be considered. When the arch is high and narrow, the mucous membrane is difficult if not impossible to transfer. When closure is obtained in this type, it is not entirely satisfactory. In a limited number of cases where the cleft is not too wide or the arch is not too high, it is possible to elevate sufficient nasal mucous membrane from the floor of the nose to suture it in the midline. It has not been entirely satisfactory for us. We feel, however, that the skin graft reduces the possibility of tissue failure to a minimum and preference is made of its use.

TYPE IV—SINGLE COMPLETE CLEFT OR UNILATERAL LIP-JAW PALATE SPLIT

When conditions permit, the lip is closed soon after birth. This produces a fusion of the alveolar cleft. Rarely, in this type, is the vomer rudimentary. As a rule, it is well developed and attached to the longer side and its mucoperiosteum can be used to close off the nasal chamber.

In the presence of a well developed vomer, lying on a plane and articulating with the palatal process, its mucosa may be separated from the bone and reflected like the open page of a book. This leaves the vomer devoid of its mucosal covering. The palatal mucous membrane on the short side

FIG. 17.



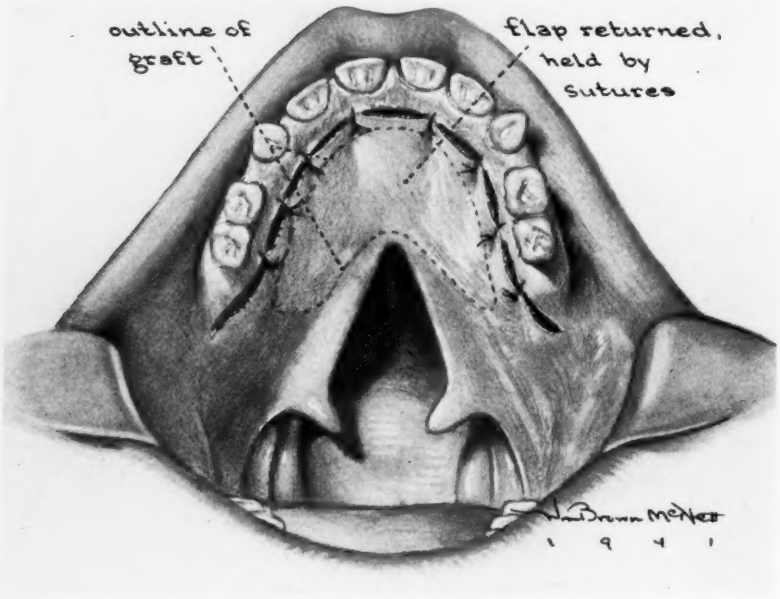
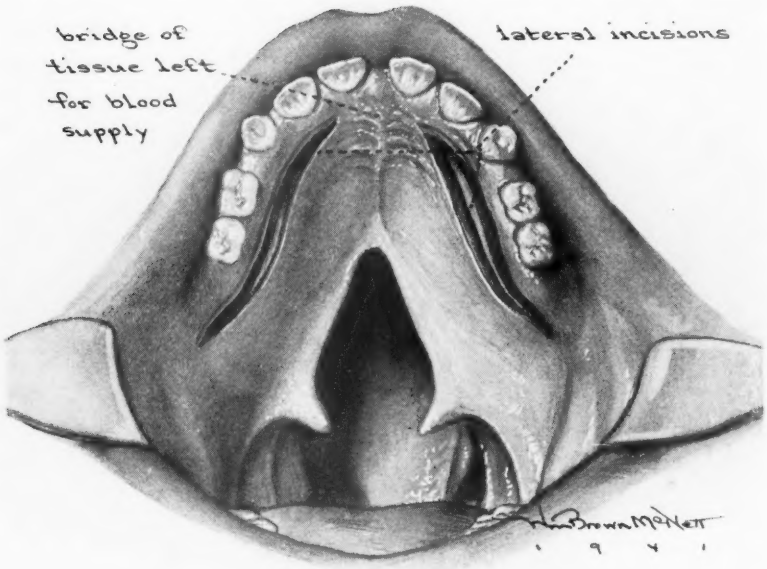


FIG. 18.

FIG. 17.—Flap elevated—Skin graft sutured in place.

Fig. 18.—Flap with skin graft resutured in place.

FIG. 19.



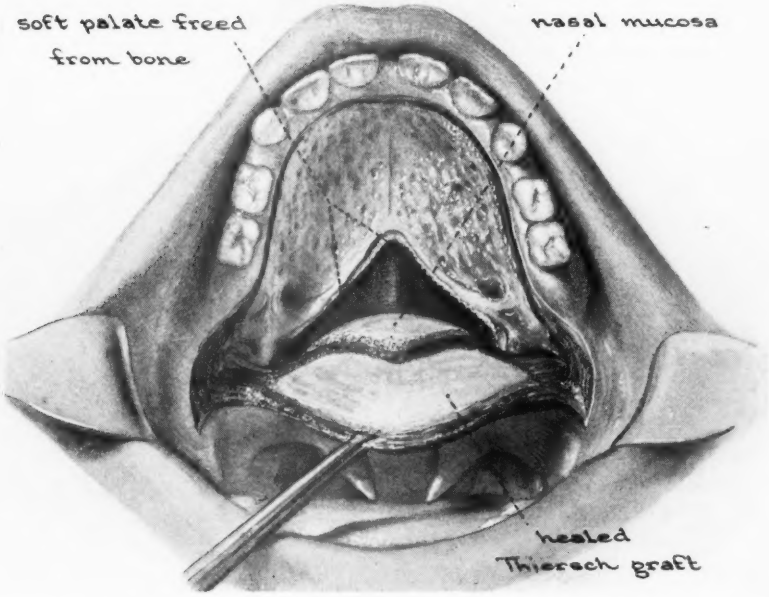
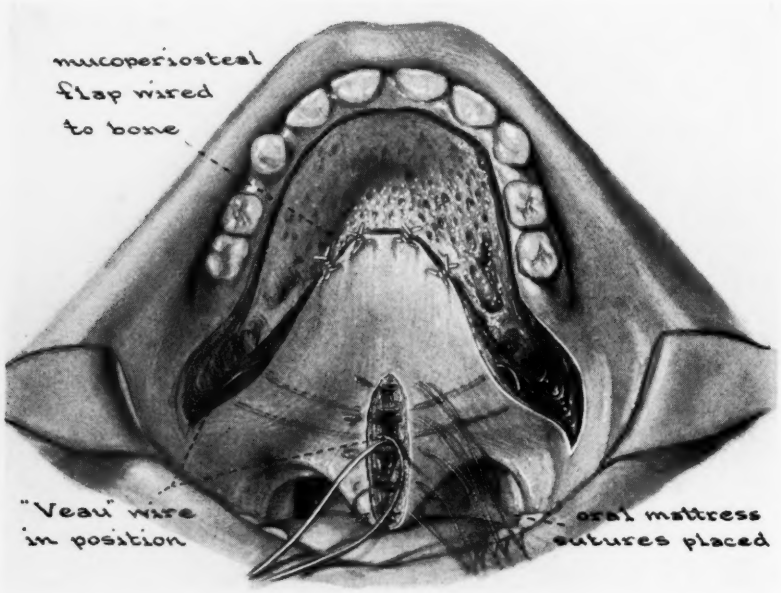


FIG. 20.

FIG. 19.—Method B—For elevation of the mucoperiosteal flap.

FIG. 20.—Flap elevated showing a successful skin graft in a cleft of the soft palate.

FIG. 21.



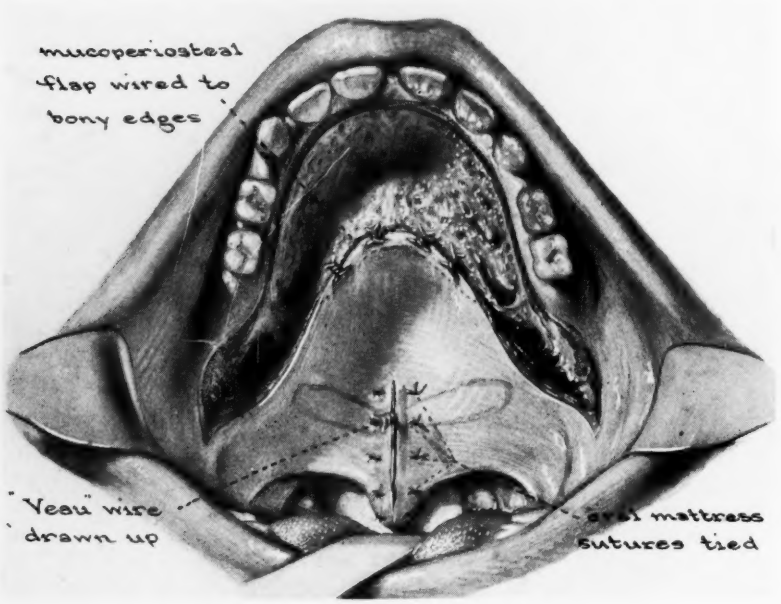


FIG. 22.

FIG. 21.—Final stage of the "push-back" operation in cleft of the soft palate.

FIG. 22.—Final stage of the "push-back" operation.

is elevated one-quarter inch along the margin of the cleft and the vomer flap is tucked into this recess. This brings the two raw surfaces into contact in which position they are immobilized with mattress sutures. The triangular cavity thus created is packed with iodoform or xeroform gauze, and held in place by a wire around the teeth for at least ten days. This area granulates progressively to the surface, effectively solidifying the anterior third of the palate (Figs. 1, 2, 3, 4, 5 and 10).

The operative sequence for correction in the presence of a well developed vomer is as follows: About the second or third year, or later, the vomer flap is reflected as described, and the area allowed to fill in. In from five months to two years later, a first of a two-stage "push-back" operation is performed. This consists of a long lateral incision on either side; the posterior palatine vessels are divided and the flaps raised (Fig. 25). If they blanch, and if very thin, we immediately suture them back into place. If the flaps are of normal thickness we suture in place skin grafts and then suture the flaps back in place. Three to ten weeks later, the "push-back" operation is performed. The flaps are elevated with their adherent skin grafts, carried backward and fixed. The pattern of this reconstructed palate resembles that of Smith, Ganzer, Halle-Ernst, Limberg and Wardill (Fig. 26).

It should be noted here that the filled-in area, bounded by the vomer flaps, remains untouched. Incisions for the "push-back" flaps are made only when the bony palate has been unmistakably outlined with a needle. This gives a bony floor for the flaps on either side of the vomer area, and the "push-back" operation is completed essentially the same as previously described.

To summarize briefly: The vomer flap is raised and sutured "leaf-of-the-book-wise" to the opposite palatal flap. The space formed is packed and allowed to granulate to the surface. We strongly stress this phase of the operation, because the anterior part of the hard palate has automatically repaired itself without disturbing any of the palatal tissue.

Five months after the vomer-mucoperiosteal transplant, the tissue in this area is usually well organized and the flaps may be elevated and skin graft inserted. Three to eight weeks later, the "push-back" operation is performed. The order of the repair is as follows:

1. The nasal sutures are inserted but not tied.
2. The Veau suture is inserted but not tied.
3. The nasal sutures are now tied.
4. The oral sutures are inserted but not tied.
5. The Veau suture is now tied by twisting the ends, thus approximating the two halves.
6. The oral sutures are now tied.
7. Retroposition is effected, and the palate is anchored in its new position with the wire sutures as previously described.

The bony palate is covered with iodoform gauze, and the latter is held in place with silver wire to permit granulation across this space.

The unilateral lip-jaw palate split, with a rudimentary vomer, is rare, but in such cases the repair may be made by either of two methods:

1. The Langenbeck operation is performed as a preliminary step, with or without a skin graft, as conditions warrant.
2. Use the method of Ganzer, modified by Limberg, and popularized by Wardill (Fig. 24).

We prefer the Langenbeck method of anterior closure followed by the V-"push-back" operation.

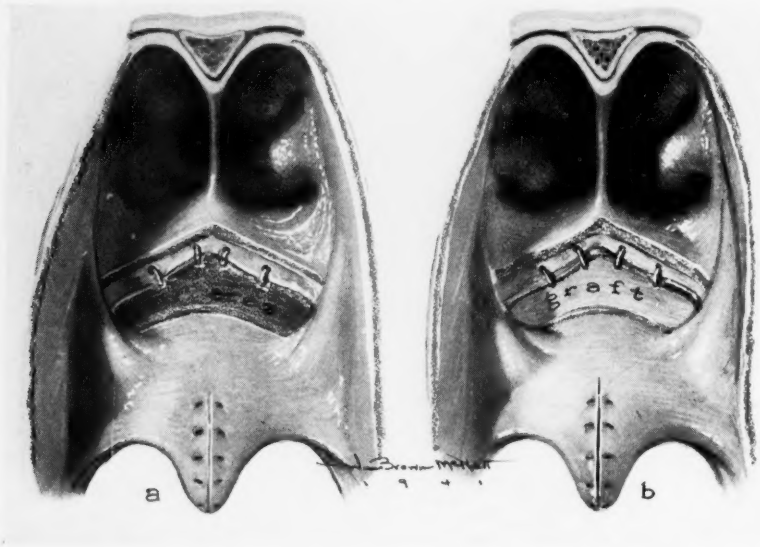


FIG. 23.—Nasal surface after the "push-back" operation. (a) Without skin graft. (b) With skin graft in place.

If the flaps permit, the grafts are inserted at the same time the palatal mucous membrane is raised. If, on the other hand, the tissue is very thin and blanches, a three-stage operation is automatically resorted to in completing the Langenbeck procedure. Since a short palate now exists, the V-"push-back" operation is performed, much the same as shown in Figure 26, to obtain velopharyngeal closure.

TYPE V—DOUBLE COMPLETE CLEFT OR BILATERAL LIP-JAW PALATE SPLIT

The method of closure is by reflecting of one or both vomer flaps of mucous membrane outward as the open pages of a book (Figs. 6 and 7). It is easier to do this bilaterally at once, and not in stages. Some authors believe there is danger of losing the vomer if this is done. However, our experience has not borne this out.

Upon the first examination of a cleft palate, soon after birth or in infancy, the vomer may appear to be only a remnant. A year or so later,

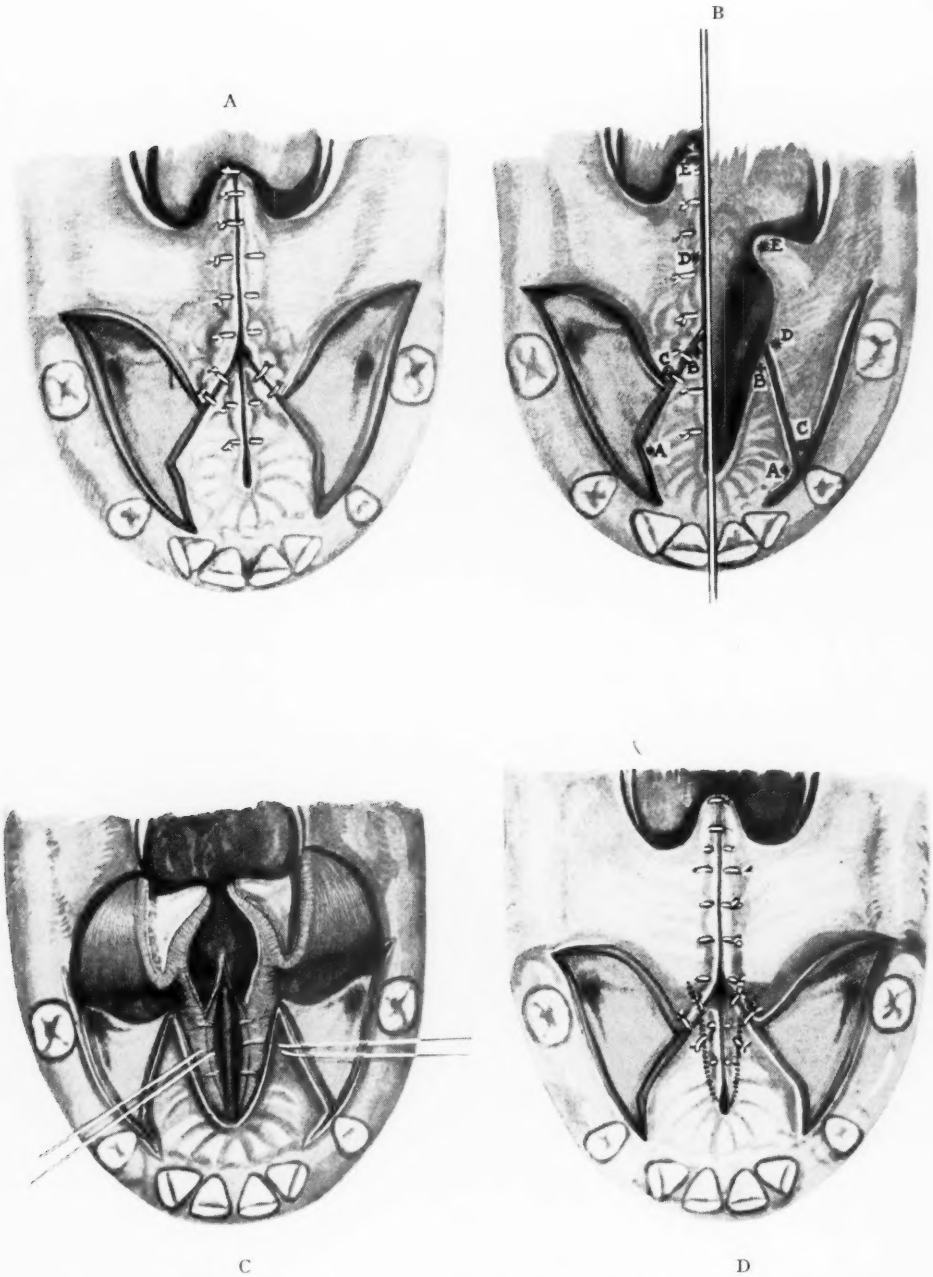
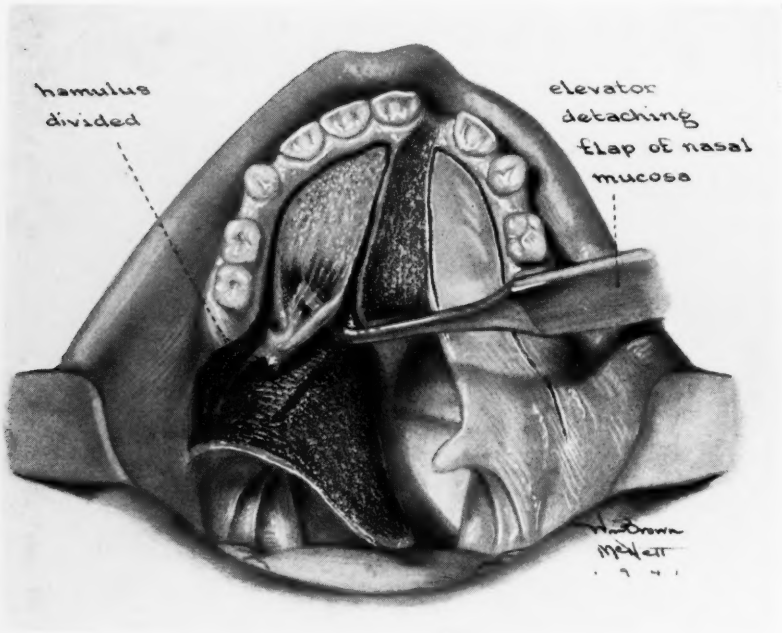


FIG. 24.—Wardill's method of operation. (A) Completion of the suture line. (B) Illustrates diagrammatically how, by cutting flaps in the method described, a form of VY advancement of the velum takes place. The letters indicate corresponding positions before and after operation. (C) The mucosa from the nasal surface of the hard palate is united to the vomerine muscosa. The situation of the stay sutures is shown. (D) Repair completed. The dotted line shows the approximate of the united nasal mucosa. (British Journal of Surgery, 25:1937)

FIG. 25.



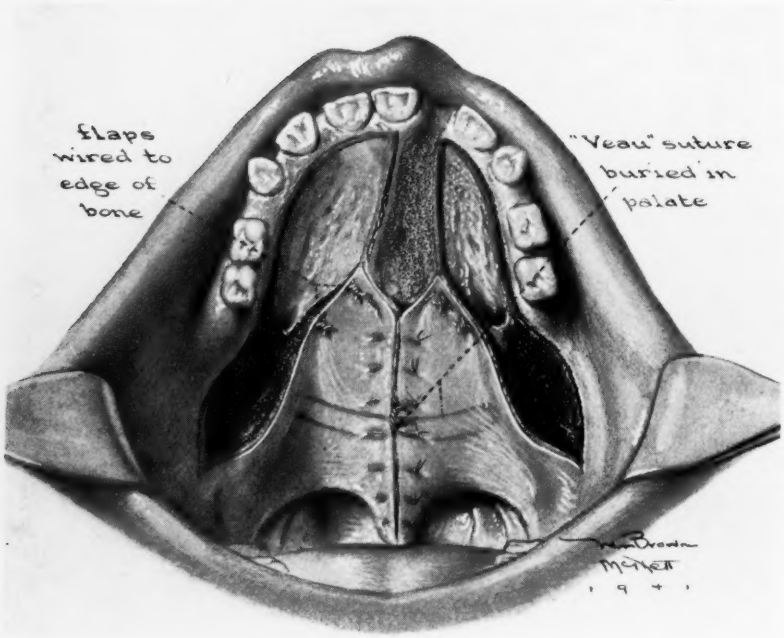


FIG. 26.

FIG. 25.—Elevation of flaps in preparation for skin graft in single lip-jaw palate cleft. Note how a portion of the nasal mucous membrane may be elevated.

FIG. 26.—Completed second stage of the "push-back" operation in single, complete lip-jaw palate cleft.

FIG. 27.

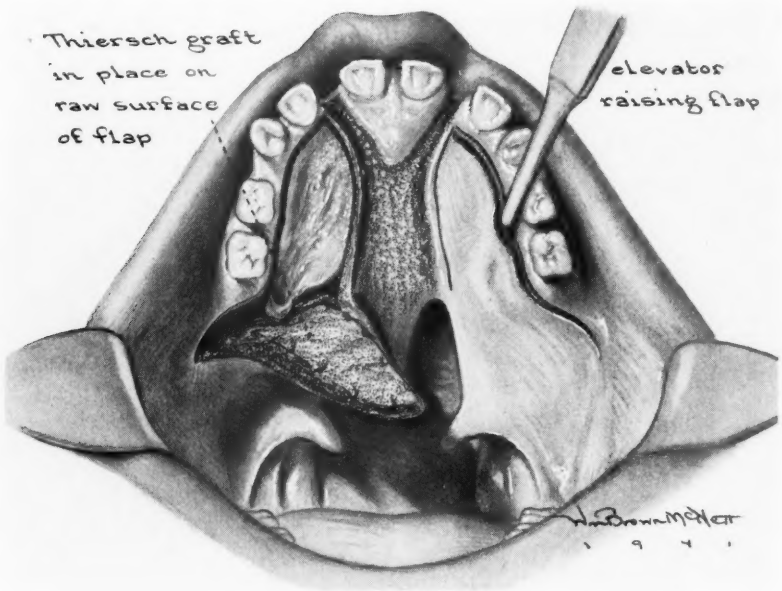


FIG. 28.

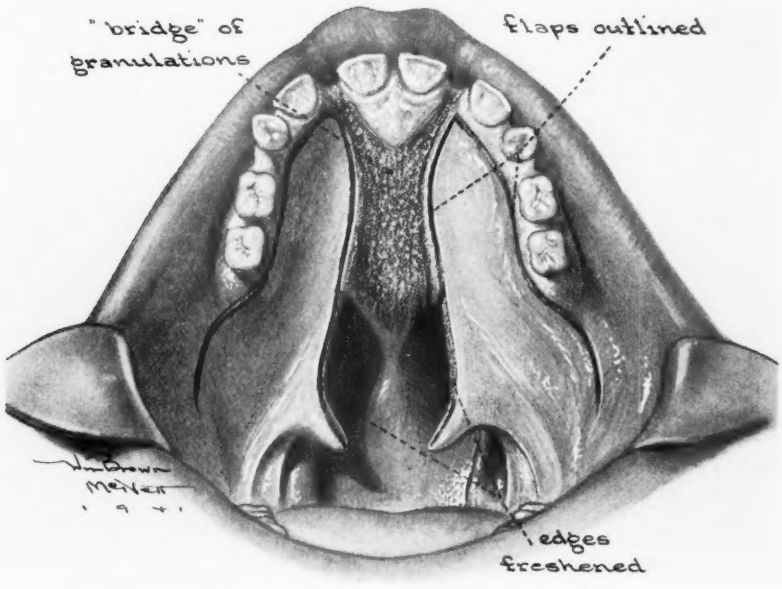


FIG. 27.—Raising of flaps and skin grafting in first stage of the "push-back" operation.

FIG. 28.—Incision for flaps in the final stages of the "push-back" operation.

one is often surprised to note that, in many cases, the vomer has developed to a point where the flaps may be utilized.

We are mindful of the additional stage-operation required, when the vomer flap technic is employed, but it so greatly simplifies the final or "push-back" operation that we feel it is indispensable. When the gauze is removed in ten days or two weeks, and the cavity has begun to fill in, it is smooth and rapidly blends with the contiguous surface of the palate (Fig. 27).

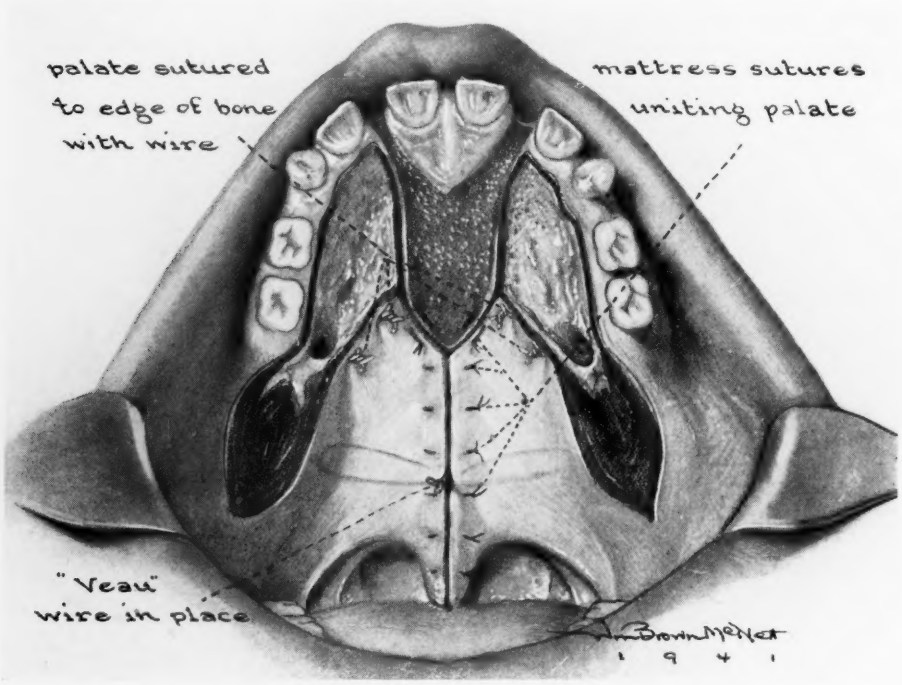


FIG. 29.—Demonstrating the completion of the final stage of the "push-back" operation in double cleft palate.

TYPE VI—COMPLETE BILATERAL CLEFT WITH RUDIMENTARY VOMER

The vomer is not available for use.

We have not been able to use Veau's method of pulling the nasal mucous membrane over for constructing a nasal lining in a large percentage of cases. In the high narrow arch, we have found it to be an impossibility. It may be accomplished in a low, wide vault, where the field of operation is much larger and the tissues are more accessible. Furthermore, when this procedure is employed, it is of value only when the Langenbeck, or similar operation, is performed for final correction. If further retrodisplacement is anticipated, the nasal mucous membrane will have to be supplemented. The skin graft, therefore, is the method of choice in these cases.

This is not intended as a criticism of Veau. On the contrary, we agree with him, as mentioned previously, that the necessity of a nasal lining is

axiomatic, but we feel that the use of the skin graft accomplishes this and permits the retrodisplacement necessary for a successful "push-back" operation.

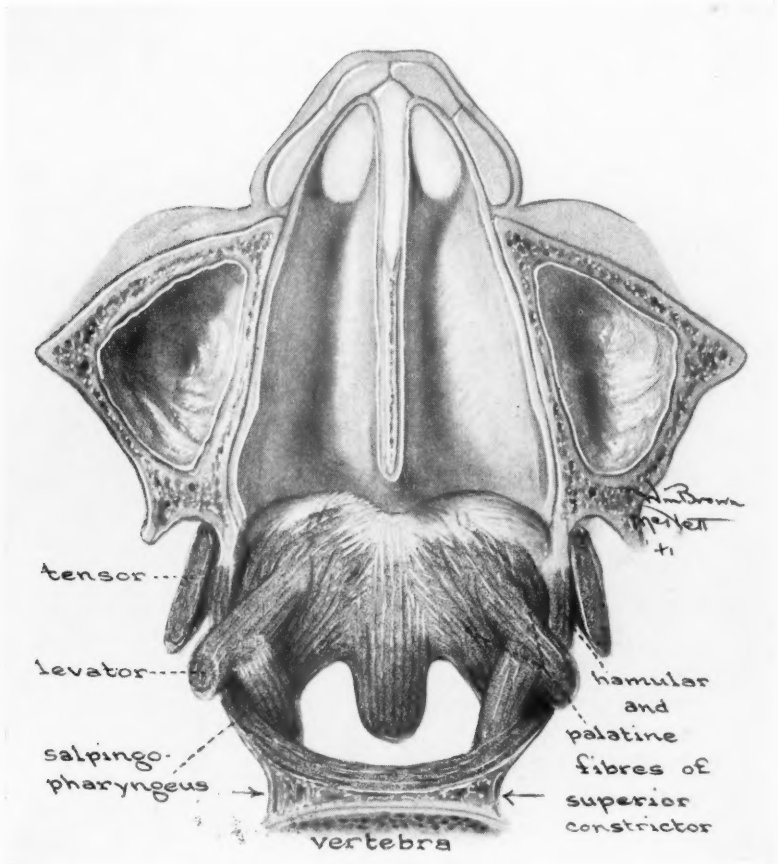


FIG. 30.—Demonstrating the position of the superior constrictor at rest. Note the palatine fibers of the superior constrictor which cause the shut-off.

SECONDARY REPAIRS

We have, in former papers, dwelt at length on the shortcomings of the mucoperiosteal and osteoplastic methods of cleft palate surgery. We feel, therefore, that mention of our methods of full correction of these previously operated cases is necessary. We classify these palates as operative successes but speech failures. We are mindful of the fact that the other surgeon's successes are not seen by us. We seldom see a palate which had been repaired by the Davies-Colley or Lane methods, where the tissues are in a state of sufficient vitality to risk further surgical correction. In the cases where we tried a "push-back" operation for correction of speech, little or no improvement resulted. We have twice successfully performed the "push-back" operation after a Brophy osteoplastic repair. We confess

that we have seen speech failures after a "push-back" operation. In such cases, the soft palate was not sufficiently separated from the hard palate structures to permit full retroposition. Many of our own Langenbeck repairs, performed years ago, have been functional failures.

The procedures for correcting these speech failures vary with the previous types and number of operations. Generally speaking, a modified

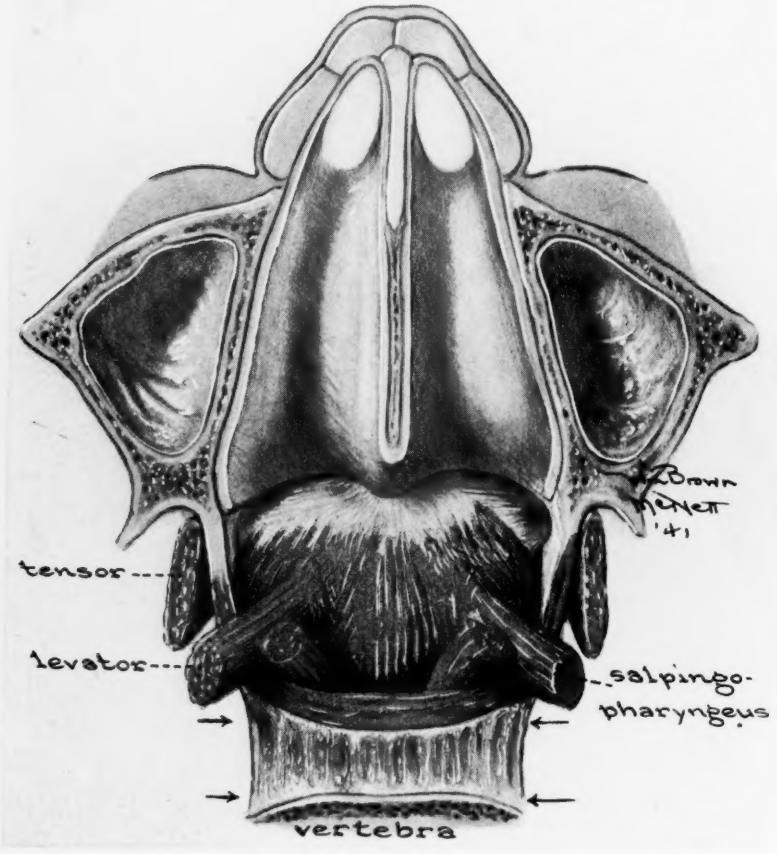


FIG. 31.—Demonstrating the position of the superior constrictor when contracted to produce the shut-off.

"push-back" forms the basis of correction on all patients who still have a palatal insufficiency and speak with the characteristic nasal tone. These secondary corrections have been very gratifying and all cases have been improved.

It is important to carefully plan the operation in each case so as to obtain maximum correction with minimum surgery. The plan is based on factors, the presence or absence of which influence the efficiency of the operation—the most important is the amount of bony palate present and the degree of vomer development.

Using a sharp needle, the edge of the bone is followed completely around the palate, automatically outlining the flaps.

The first stage consists of elevating the mucoperiosteum; dividing the palatine vessels (if not done at the previous operation). Next, insert the

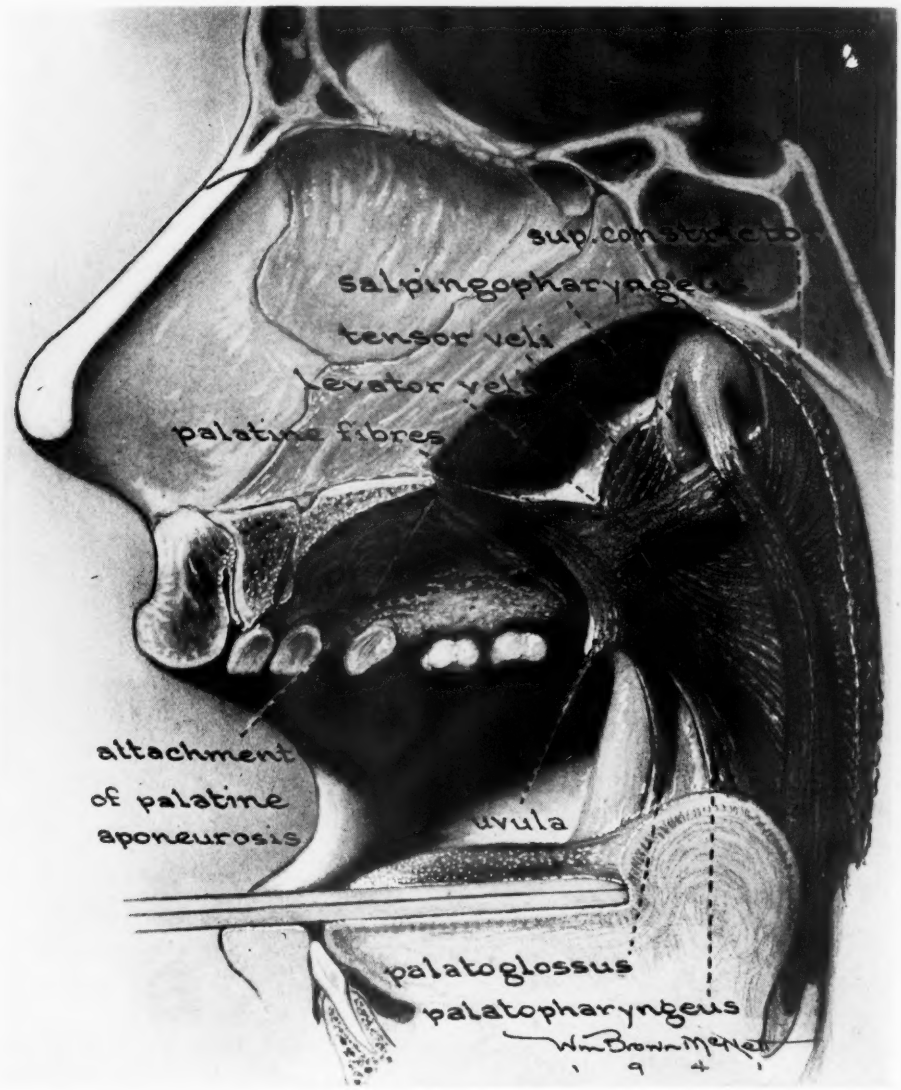


FIG. 32.—Lateral view of the position of the palate muscles in a cleft involving the bony palate, before operation.

skin graft if it is to be employed. It is very difficult to insert skin grafts in cases that have been operated upon many times before. Fortunately, the marked overproduction of fibrous tissue, existing from repeated trauma, is not so prone to contracture, and the skin grafts are not as necessary.

The second stage of the push-back operation is performed three to ten weeks later.

The hamular process is divided on each side, and the soft palatal tissues are completely separated from the posterior border of the hard palate. The lateral tissues are bluntly dissected out until the internal pterygoid muscle is reached, at which time there should be sufficient retroposition of

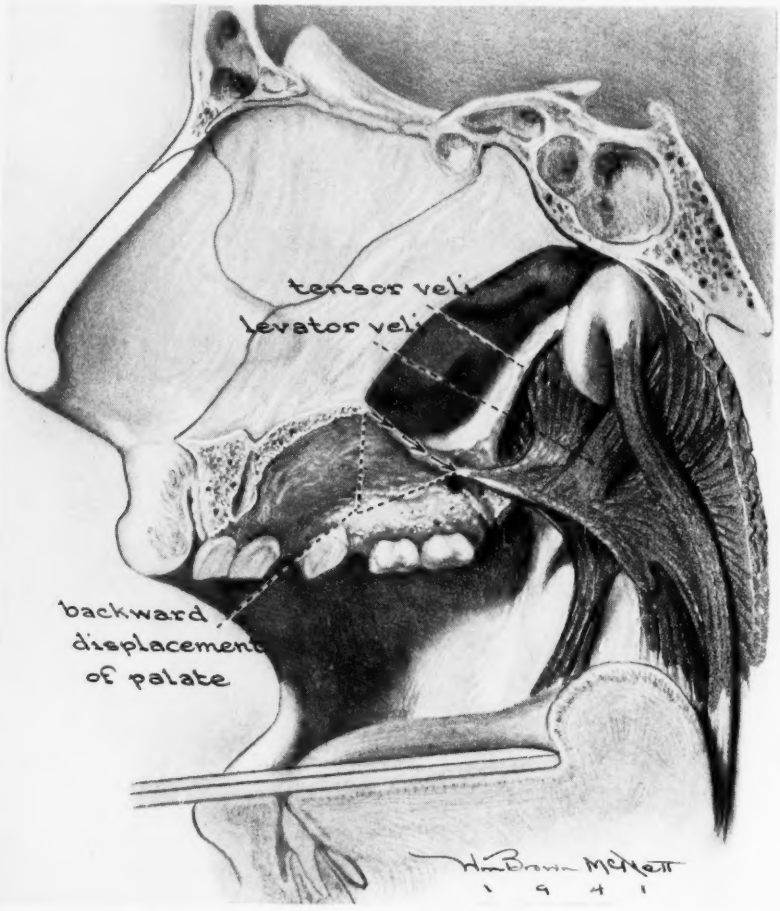


FIG. 33.—Lateral view of the position of the palate muscles in a cleft involving the bony palate, after the "push-back" operation.

the tissues. The flap or flaps are then sutured as previously described in Figures 21–26.

It is to be emphasized that in these secondary repairs it is necessary that overcorrection be made.

SECONDARY PALATAL DEFECTS

All surgeons performing cleft palate operations have, at some time or other, been disappointed by having repeated failures in attempting to close secondary holes in the palate. The conventional operation, using lateral

relaxing incisions to allow flaps to close the defect, usually fails. The area above the repair forms a gutter for the accumulation of débris, and separation ensues. The presence of a mucous membrane-lining reduces the number of failures. The method of "turn-over," as advocated by Davies-Colley, has been disappointing. Illustrations of this method are very convincing, but successes in our hands have been few. Wherever possible, the mucous membrane is brought over, as shown by Veau. Unfortunately, the mucosa has not always been readily accessible. Our method of skin grafting, followed subsequently by lateral incisions and closure, has given more encouraging results.

CONCLUSIONS

Operations designed for the simple closure of a cleft palate are not adequate for producing articulate speech.

The "push-back" operation, in our hands, has increased the number of satisfactory speech results in cleft palate patients. This is particularly true in patients who have had previous operations, which resulted in but little speech improvement.

The surgical correction is based on findings, as a result of original investigation, and in the anatomy of the velopharyngeal mechanism.

The "push-back" operation establishes the normal muscle and palate position, so that proper velopharyngeal closure is made possible.

The use of vomer-flap transplant in cleft palate surgery has materially reduced the incidence of residual defects in the alveolar ridge. We feel that our modification of the method, by producing granulation with packing placed over the vomer flap, is essential if the "push-back" operation is employed.

The skin graft has produced a heavier flap of tissue, and minimized tissue contraction following palatal surgery. It has also given us a higher percentage of closure in correcting secondary palatal defects.

Nearly all cleft palates show some degree of bone deficiency, and while each type requires a different operation, our basis of all corrective surgery is the "push-back" operation, with variations for the individual case.

We do not advocate the use of pharyngoplasty as a routine procedure nor do we encourage posterior pillar surgery. Pharyngoplasty may be of great value in cases where the superior constrictor will not develop and produce Passavant's ridge or ring. There are cases that are surgically non-corrective because of insufficient tissue. The greatest gain in these cases is obtained by the use of an obturator. If, however, the "push-back" operation can be effected, even with a remaining defect in the anterior part of the palate, this is done, and the defect is covered with a small obturator.

THE MECHANISM OF SHOCK IN INTESTINAL STRANGULATION

AN EXPERIMENTAL STUDY

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FEW SURGICAL EMERGENCIES present a graver picture of shock than that seen in intestinal strangulation, especially if a long loop is involved, or the symptoms have persisted for several hours or more. The rapid, feeble pulse, the pale and often cold extremities, the low blood pressure, the anxious yet worn expression, all suggest a seriously decreased effective blood volume. When the peritoneal cavity is opened and the surgeon observes that the distended intestinal loops are bathed in thin, blood-tinged fluid, he is presented with direct evidence that the blood volume is reduced; but when the turgid, discolored loop is resected and opened to display the foul-smelling, blackened contents, it is difficult to resist the temptation to incriminate the loop contents (with their "toxins") as the most important, if not the sole initiating cause of the shock picture.

Experimental studies, too numerous to mention in detail, have been carried out for the purpose of determining the cause of death in closed intestinal loop obstruction. These, in the main, have served to focus attention on the extremely toxic nature of the contents of the closed loop (Whipple, Stone, *et al.*[16]). They have demonstrated that when cell-free extracts of the loop contents are injected *intravenously* into suitably prepared animals, the recipient animal becomes quite ill, shows signs of shock similar to that seen on histamine injection, and usually dies in profound collapse. Moon[14] (1938) has indicated that these animals show pathologic changes similar to those seen in patients dying from shock, and has concluded that such studies provide strong evidence that shock can best be explained on the basis of generalized damage to all capillaries as a result of direct action of a toxin.

Few investigators interested in intestinal strangulation have paid close attention to the extent of plasma loss in this condition. There are two notable exceptions: Aird[1] (1937) placed a rubber bag around a loop of small bowel in cats, then strangulated the loop by tying a ligature around the neck of the bag tight enough to make the mesenteric pulsation just palpable. The blood loss was measured by comparing the weight of the bag plus the contained blood and intestinal loop with the same length of normal bowel. The results of nine experiments demonstrated that 50–80 per cent of the blood can be shunted from the effective circulation within 18–24 hours by this

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method, and that the loss of blood varies directly with the length of loop strangulated.

Scott[15] (1938), working in Wangensteen's laboratory, has published an excellent paper on the cause of death in intestinal strangulation. In an experimental study on dogs, in which various types of arterial and venous occlusion of the blood supply to loops of small intestine was produced by ligation, he found that in partial occlusion of arterial and venous systems the blood loss was 35 per cent; complete occlusion of blood supply, 22 per cent; complete occlusion of artery with patent vein, 20 per cent; and complete venous occlusion with patent artery, 55 per cent. Scott concluded that: "The loss of blood in strangulation obstruction has been calculated and found adequate, with the venous types of occlusion at least, to account for the shock and death with occur."

Gendel and Fine[7] (1939), in their paper on plasma loss in intestinal obstruction, presented data on three dogs with a strangulated intestinal loop. By the dye method, these animals lost 30.8, 64.2 and 51.4 per cent of their blood volume during four hours of strangulation, respectively.

In our present studies on shock, we have been able to make a series of observations on plasma loss in intestinal strangulation, and to correlate this loss with the alteration in actual plasma volume of animals before and during the shock state. These are recorded below, with remarks on the relation of such data to the general problem of the initiating factors in shock.

Experimental.—The first few experiments demonstrated that if a small loop of the lower ileum was strangulated, the animals lived for 18 hours or more. Thereafter, the experiments were conducted in the following manner: Healthy dogs were used. After a 36-hour fast, the plasma volume was determined by the Gregersen[9] dye method (1937) after the modification which employs the photo-electric colorimeter (Gibson and Evelyn,[8] 1938). At this time, determinations of total plasma chlorides, nonprotein nitrogen, and hematocrit were made. That same evening, under evipal anesthesia adequate for a short celiotomy (usually 40–50 mg. per kilo), and with strict asepsis, a loop of lower ileum, 14 inches in length, the lower end of which was about six inches above the ileocecal valve, was ligated with a rubber band (5 Mm. in width). The ligature was drawn tightly enough to produce obvious obstruction to venous return from the loop of bowel, but only tightly enough to diminish slightly the arterial inflow. The intestines were returned to the peritoneal cavity, and the abdomen closed in layers, with silk sutures. By the time the skin was closed, the animals were usually coming out from the anesthesia, so the total anesthesia time was usually one-half hour or less. Evipal was employed as the anesthetic agent, rather than ether, first, because it probably does not affect the plasma volume as much as does ether (McAllister,[12] 1938, and Hamlin and Gregersen,[10] 1938), and, secondly, because it gave the advantage of a very short anesthetic period. It is felt that the shock which subsequently developed could not have been influenced greatly by this procedure, in itself, and could not very plausibly be

attributed to the brief anesthesia. This should obviate the criticism of Moon[14] (1938) that in certain experimental studies, the anesthetic may have been the cause of shock.

The next morning, 12–14 hours later, the animals were always in varying degrees of "shock." The pulse was always rapid (150–220 per minute) with a weak pulsation in the peripheral arteries; the extremities were often cold; temperature (rectal) was usually elevated 1°–2°C.; respirations were normal; more often than not, these animals could be induced to jump out of their cages. Only one dog was obviously moribund at this stage.

FIG. 1.—The appearance of a strangulated loop of bowel, contrasted with normal bowel after 14 hours of strangulation.

At this time, a second plasma volume determination was made, and, at the same time, the hematocrit, plasma protein, chlorides, and nonprotein nitrogen were determined. With local anesthesia, the blood pressure was measured with a mercury manometer from a cannula in the left femoral artery. The animals were then anesthetized with various anesthetic agents (these studies were reported in detail elsewhere [Evans and Beecher,[4] 1941]); death ensued in 30 to 200 minutes. After death, the peritoneal cavity was opened carefully. The free blood-tinged fluid was collected with sponges, the amount and character recorded, and its protein content and hematocrit determined. A careful necropsy was then performed on each animal.

Necropsy Findings.—Figure 1 illustrates the usual appearance of the strangulated loop. The amount of free peritoneal fluid varied from 63 to 329 cc. The small bowel above the strangulated loop appeared normal,

sometimes being slightly distended with fluid. The stomach and duodenum were always normal in appearance. The spleen was always contracted; in three instances there were small hemorrhagic infarcts in this organ. The liver, lung, heart, kidneys, and adrenals were normal. In no instance did the lungs show evidence of edema, such as that described by Moon,[14] (1938). In no instance was the pericardial lymph stained with the dye (T-1824) used in the determination of the second blood volume. This finding is in contradistinction to the findings of Freeman, *et al.*[6] (1941), who induced "shock" by continuous adrenalin infusion. This has been discussed elsewhere in connection with the validity of the Gregersen dye method for plasma volume determination in the shock state (Evans and Hamlin,[5] 1941). It may be stated here that in all but one experiment, the disappearance slope of the dye curve has been the same in the normal and in the shock state for the same dog.

As a final step, the strangulated loop was opened, its contents collected and measured. The loop contents were always dark red-black in color, possessed an extremely foul, permeating, sometimes nauseating odor, and resembled more closely laked whole blood, than plasma.

Experimental Observations.—1. In Table I are shown the chemical and physiologic data on these animals, in the normal state, and after 12–14 hours of intestinal strangulation. For brevity, representative data are shown for only 10 of the 29 dogs so studied.

TABLE I

CHEMICAL AND PHYSIOLOGIC DATA IN TEN ANIMAL EXPERIMENTS

Dog No.	63	79	81	102	104	113	126	129	122	144
Weight	15.0	16.3	10.0	9.4	9.1	13.0	14.2	13.7	16.5	10.1
Hematocrit										
Before	47.0	38.0	34.0	41.0	41.5	42.8	44.2	46.8	43.6	58.3
After	53.0	48.5	42.5	58.3	53.8	48.7	53.2	48.9	61.5	65.0
Plasma Protein										
Before	5.35	6.63	5.97	6.31	....	....	6.33	5.85	6.35	5.42
After	5.29	6.60	5.87	6.07	5.48	6.32	5.70	5.66	6.52	6.31
Chlorides										
Before	106	101	110	106	....	128	120	120	120	116
After	108	103	102	98	120	132	108	124	116	120
Per Cent of Plasma Lost	—38	—25.3	—45.9	—34.8	—31.4	—23.4	—40.8	—27.1	—45.4	—35.2
CC. Plasma Lost, Dye Method	268	231	302	161	134	155	283	147	436	178
Fluid Collected										
Peritoneal Cavity	225	175	304*	148	119	158	155	98	329	160
Loop	50	10	....	152	65	174	48	82	95	50
Protein Content Peritoneal Fluid	4.21	4.46	....	....	4.80	6.89	4.56	8.30	4.77	5.04
Initial B. P. in Shock Mm. Hg	65	128	72	78	74	57	88	49	65	35
N. P. N.										
Before	....	....	....	....	....	....	20.0	30.0	26.4	30.0
After	....	....	....	....	....	....	36.4	42.2	44.5	69.0

*Total

It will be noted first that there has occurred during the experimental period a material decrease in actual circulating plasma, ranging from 25.3 to 45.9 per cent. The blood chlorides remain unchanged; this was to be expected because these animals do not vomit, so no gastric juice is lost. The hematocrit rises from 6.0 to 17.9 per cent; this hemoconcentration indicates a predominant loss of plasma rather than whole blood. The plasma protein

concentration is unchanged, indicating that if fluid is drawn from the extravascular spaces or tissues into the blood stream tissue proteins come with it. The nonprotein nitrogen rises very slightly; this may indicate a decrease in kidney function or perhaps the absorption of blood from the peritoneal cavity.

In Chart I, the initial blood pressure (after the 12–14-hour strangulation) is plotted against the decrease in plasma volume. It will be noted that the blood pressure appears to be fairly well maintained until the plasma loss

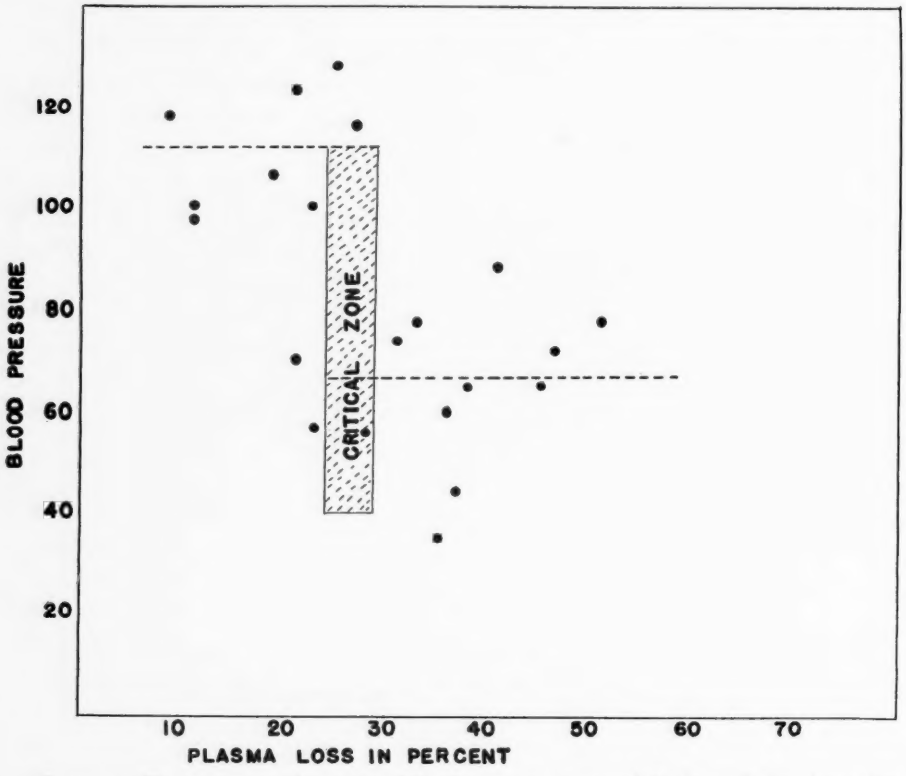


CHART 1.—The apparent maintenance of blood pressure at normal levels until the plasma loss exceeds 25-28 per cent.

exceeds about 28 per cent. If a greater loss occurs, the blood pressure is obtained at "shock" levels.

An analysis of the data demonstrated that the pulse rate was always elevated, whether the plasma loss was in the neighborhood of 20 or 35 per cent. There appeared to be no close correlation between plasma loss and pulse rate.

THE RELATION OF THE VOLUME OF FREE PERITONEAL FLUID TO PLASMA LOSS

The free peritoneal fluid collected from these animals with strangulated loops had these characteristics: It was slightly pink to red in color, and contained varying numbers of red blood cells; when centrifugalized, the

hematocrit was low, 2.1 to 6.2 per cent. The supernatant fluid resembled the animal's plasma. If sodium thiocyanate had been injected (to determine extracellular fluid volume) the thiocyanate concentration of the animal's plasma was the same as that in the peritoneal fluid. The protein concentration was slightly lower than that in the plasma. The odor was that of the animal, never like that of the loop contents. If allowed to stand in a test tube for several minutes, a solid clot formed throughout the tube of free peritoneal fluid, just as in heparinized plasma to which has been added a sufficient amount of thrombin.

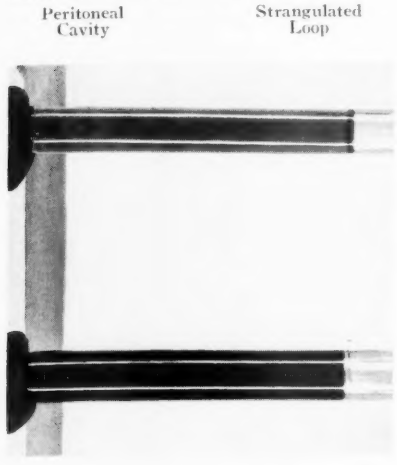


FIG. 2.—The centrifugalized free peritoneal fluid contrasted with that from the strangulated loop.

From these observations it has been concluded that the free peritoneal fluid in these shock animals closely approximates *plasma*. Figure 2 illustrates the centrifugalized free peritoneal fluid contrasted with the fluid from a strangulated loop.

In Table 1 and Chart 2 is presented a comparison between the amounts of free peritoneal fluid collected, (with its protein concentration), and the decrease in plasma volume as measured by the dye method. It will be observed that in most of the experiments practically enough free peritoneal fluid was collected to account for the plasma volume decrease. When the volumes of the loop contents and free peritoneal fluid are considered together (Chart 2), it will be seen that the plasma seems to have been lost "locally," *i.e.*, in the loop or into the peritoneal cavity, rather than "generally" from the capillary bed of the entire body. The significance of this observation will be pointed out below.

THE TOXICITY OF THE FREE PERITONEAL FLUID

No one who has opened a strangulated loop of bowel could fail to have been impressed by the obvious toxic nature of the loop contents. The odor is so offensive, so fecal in character, that it is easy to imagine the serious consequences that must result should this material be asborbed unchanged into the blood stream. But there rests the problem: Do these substances in the strangulated loop get into the general circulation?

Absorption from the loop of bowel can take place only in three possible ways, namely, by the loop lymphatics, by the loop venous system, or by passage through the serous coat and then transperitoneally, to be absorbed either by the normal mesenteric vessels or by the lymphatics of the general peritoneal cavity.

In a strangulated loop, the venous and lymphatic return of the loop are obstructed; absorption can, therefore, take place only transperitoneally. If

this be true, then the only route by which toxic products in the strangulated loop can enter the general circulation is to pass through the serous coat of the strangulated bowel, into the fluid contents of the peritoneal cavity, and then into the general circulation *via* lymphatics or mesenteric circulation.

On this basis, the following experiments were carried out. Intestinal strangulation was produced in the described manner. When the dog was in quite severe shock, the free peritoneal fluid was collected under local

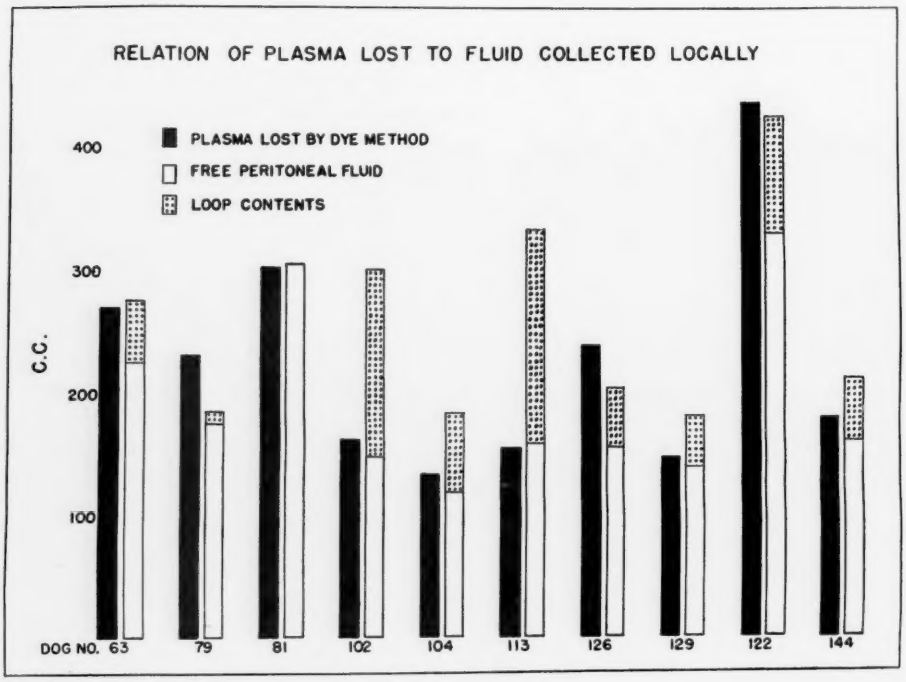
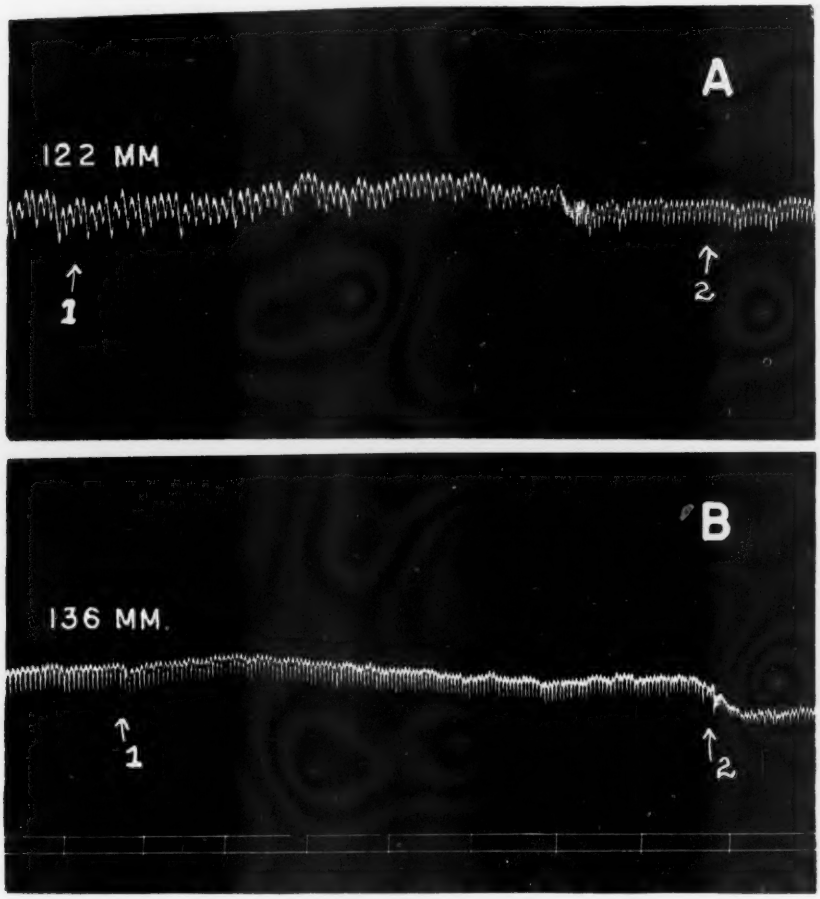


CHART 2.—The relation of plasma loss, as measured by dye methods, to fluid collected in the peritoneal cavity and in the strangulated loop.

anesthesia through a small incision in the abdominal wall, by aspiration and suction. Clotting was prevented by a small quantity of two per cent sodium citrate. About 100 cc. of peritoneal fluid was collected from each of three dogs in shock. This peritoneal fluid was then diluted with equal parts of 0.9 per cent NaCl solution and injected intravenously into suitable recipient animals. In Graph 1A is shown the kymographic tracing of the blood pressure curve, shortly before, during and after the intravenous infusion of 75 cc. of free peritoneal fluid taken from a shock dog. The response was a slight rise in blood pressure during the infusion. In Graph 1B is shown the kymographic tracing of the blood pressure curve of a normal dog under sodium amytal anesthesia, 50 mg. per kilo, during the intravenous infusion of 100 cc. of peritoneal fluid taken from another animal in shock. In none of three such experiments was there any evidence of the presence of a depressor substance in the free peritoneal fluid of these shock dogs. Dogs given such

intravenous infusions appeared normal when they had recovered from the barbiturate anesthesia.

These findings corroborate those of Scott.[15] He found that intravenous infusion of peritoneal fluid from dogs with intestinal strangulation was without effect on normal dogs if the peritoneal fluid came from animals that died without gross rupture of strangulated loops.



GRAPH 1.—A, and B. The effect of the intravenous infusion of 75 cc. and 100 cc., respectively, of peritoneal fluid on the blood pressure of normal dogs.

THE MECHANISM OF SHOCK IN INTESTINAL STRANGULATION

Discussion: In his treatise on traumatic shock, Blalock[3] (1940) has emphasized that in an intelligent appraisal of the various possible causes of shock, one must take care to differentiate the *initiating* factors from the *sustaining* and *terminal* factors. This, many writers have failed to do, especially in statements about the cause of shock in intestinal strangulation.

In the following paragraphs, there have been grouped together under the general headings of "initiating, sustaining, and terminal," the factors believed

to be important in the causation of shock in intestinal strangulation; they are thus separated because of their relation to the time-sequence during which they act. The sequence of events could be stated as follows:

A. *Initial Phase:* A loop of bowel is strangulated by torsion, a band, or caught by the neck of a sac (hernia). The venous flow is obstructed, while the arterial inflow is unimpaired. A high venous pressure develops locally in the strangulated loop, with increased capillary filtration *locally*, and when the endothelial capillary wall is damaged sufficiently, fluid and protein pour out into the lumen of the loop and through the serous coat into the free peritoneal cavity. Soon, practically pure plasma is passing through the capillary wall. The effective circulating plasma volume falls in direct ratio to the local loss of plasma, with a decreased effective blood volume (and diminished cardiac output) resulting if the condition persists.

B. *Sustaining Phase:* The blood pressure remains elevated as long as the plasma loss can be compensated for by the protective vasoconstrictor mechanism. There is still only local damage, *i.e.*, in the affected loop. When the plasma loss exceeds a certain value, *e.g.*, above approximately 25–30 per cent, the vasoconstrictor mechanism ceases to be effective because of a marked disparity between the effective blood volume and the size of the vascular bed. The blood pressure falls, and the cardiac output diminishes. If this state persists for long, the blood flow to all tissues diminishes to such an extent that *generalized* increased capillary permeability may develop.

C. *Terminal Phase:* Generalized capillary damage is attended by rapid leakage of protein and fluid from the vascular bed to the extracellular and lymph spaces; hence pulmonary edema, capillary stasis, necrosis of bowel mucosa, *etc.* During this phase, the bowel wall of the strangulated loop may be so damaged as to become permeable to any of the contents of the loop, and they pass into the peritoneal cavity; a general toxemia develops, with death ensuing.

Such data as have been gathered in the present study seem to fit well into this conceptual scheme. We know that the venous strangulation of an intestinal loop early results in local damage, with plasma loss, because that can be easily observed when the animal is still under anesthesia. At the end of 12–14 hours it can readily be demonstrated that there is a *local* loss of plasma because plasma-like fluid can be collected from the peritoneal cavity. This fluid closely resembles plasma; the extent of the plasma loss as estimated by dye methods can be readily accounted for by the amount of plasma collected "locally" (Chart 2). It, therefore, seems quite unnecessary, and somewhat illogical, to attempt to account for this plasma loss by invoking a "generalized" loss of plasma, in the initiating, and, probably, sustaining phases of shock.

The relative absence, so far as could be demonstrated by depressor response when given *intravenously*, of any "toxins" in the free peritoneal fluid of these shock dogs is presumptive evidence that in the initiating phase of this type of shock "toxins" are not important causative factors. I have

not the slightest doubt that the loop contents are extremely toxic, especially when administered intravenously or intraperitoneally. As pointed out by Gatch and Culbertson[17] (1935), however, "the crucial test (of the intoxication theory) must be the demonstration that toxic material is actually absorbed from the obstructed bowel." If it be admitted that in strangulated loop experiments the only absorption of such "toxins" is transperitoneally, it would seem, in the light of the above evidence, that this "demonstration" is still lacking.

The pathologic findings in the present group of shock dogs are decidedly different from those described by Moon and Morgan[13] (1936) with a similar shock preparation. However, in their experiments, in which evidence of generalized capillary damage was found (pulmonary edema, bowel mucosal hemorrhage, *etc.*), the animals were allowed to *die* from shock. These changes would be expected in animals dead from shock, if the "sustaining" and "terminal" phases were long enough to permit generalized capillary damage.

Although Moon and Morgan injected strangulated loop contents, and found them extremely toxic, enough so to produce death when injected *intravenously*, they did not test the toxicity of the free peritoneal fluid of their shock animals, even though they agree that when the blood and lymph channels of a strangulated loop are obstructed, absorption of toxic products must take place "in part by diffusion into the peritoneal cavity with absorption through the peritoneal surfaces."

An abundance of data on plasma and blood loss in experimental traumatic shock has led both Blalock and Phemister to the conclusion that most of the blood or plasma loss is "local" at the site of injury, and that there is only a minimal loss of plasma through indirectly damaged capillaries or into areas of capillary stasis remote from the site of injury ("traumatic toxemia"). Blalock[2] (1931) states "the observations thus far indicate that the local loss of fluid at the site of injury is the most important factor in producing the decline in blood volume and blood pressure in shock. Evidence was not found for the action of toxins in these experiments."

It would appear from the experiments recorded here that substantially the same view might be taken for the cause of shock in intestinal strangulation; that the local loss of fluid from the strangulated loop of intestine is the most important factor in producing the fall in blood volume and blood pressure. No evidence for the action of toxins was found in these experiments.

CONCLUSIONS

In an experimental study of shock produced by strangulation of a short loop of ileum, it has been found that there occurs a large loss of plasma *locally*, great enough in itself to account for the fall in blood volume and blood pressure. There was no evidence found for plasma loss from capillaries damaged by "toxins," remote from the site of injury.

It is a pleasure to acknowledge my indebtedness to Dr. E. D. Churchill, who intro-

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FLUID, PROTEIN AND ELECTROLYTE ALTERATIONS IN EXPERIMENTAL INTESTINAL OBSTRUCTION*

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In 1928, Foster,[1] in clarifying the status of acute intestinal obstruction from an experimental and clinical point of view, chose to define two arbitrary entities: (1) Acute simple obstruction of the continuity of the gastro-intestinal tract without primary vascular derangement; and (2) acute intestinal strangulation with interference to the vascular supply of the part. Thus, simple constrictions or bands about the intestine produce acute simple obstruction without vascular derangement, provided that the degree of distention of the occluded bowel is not excessive. Herniation or volvulus of a loop of intestine produces in addition to the obstruction a disturbance of its vascular tree. The multiplicity of factors that may enter into the pathogenesis of intestinal obstruction makes it imperative that each experimenter carefully assess the rôle played by the several physiologic and pathologic processes involved. For example, it is important to have information concerning the extent of the following: The plasma and interstitial volume dehydration; the disturbance of the acid-base equilbrium; the distention and ischemia of the preoccluded bowel; the vascular derangement associated with strangulation, as well as to keep in mind the regional differences in function (secretory, absorptive) and adaptability of different levels of the gastro-intestinal tract.

The present study was undertaken to evaluate, quantitatively, the changes in the plasma (T-1824) volume and the "available (thiocyanate) fluid," or roughly the extracellular fluid volume in dogs with pyloric, jejunal, terminal ileal, and colonic obstruction; to interpret, on the basis of these changes, the reliability of the hematocrit and plasma protein concentrations as indices of plasma dehydration; and to consider the rôle of certain factors in influencing the rate of development of dehydration and the severity of the symptoms in experimental obstruction.

METHODS

The obstruction of the gastro-intestinal tract of dogs was produced, under anesthesia, by tying a surgical tape one centimeter in width about the desired portion in such a manner as to occlude the lumen and yet not to produce ischemic necrosis and perforation. The degree of interference with the vascular supply in such a preparation depends subsequently upon the magnitude of the distention of the intestine proximal to the obstruction. In

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some animals, as judged by the clinical course and the postmortem gross and histologic examination, the interference with the vascular supply to the part was minimal; in others, with great distention of the preoccluded portion, the rôle of a decrease in circulation to the segment was more prominent.

The time required for operation and anesthesia was short (15 to 30 minutes) and the degree of dehydration produced was minimal (as indicated by changes in the hematocrit and plasma protein concentration). In some cases before the abdomen was closed, physiologic saline was given intraperitoneally to combat dehydration due solely to the operative procedure. In order either to induce or to minimize a rapid loss of body water by emesis, water and food were either given or withheld from the animals in the postoperative period.

Fasting blood samples were carefully collected with greased syringes to avoid hemolysis. The plasma (T-1824) volume and the "available (thiocyanate) fluid" volume (or roughly the extracellular fluid volume) were determined by the direct method of Gregersen and Stewart[2] as modified for the photo-electric colorimeter by Gibson and Evelyn.[3] The hematocrit determinations were made with heparinized blood in Sanford-Magath or Van Allen tubes, the plasma protein determinations were made by the micro-Kjeldahl technic and the falling-drop method of Barbour and Hamilton,[4] and the plasma chloride determinations by the method of Van Slyke,[5] as modified by Wilson and Ball.[6] The total amount of circulating plasma protein was obtained by multiplying the plasma volume by the plasma protein concentration in grams per cubic centimeter. The percentage changes of the plasma volume, thiocyanate volume, and total circulating proteins were based upon individual control levels. At death, a gross pathologic examination was made, and sections of the viscera were taken for microscopic study.

RESULTS OF EXPERIMENTS

Pyloric obstruction was produced in eight dogs. The findings are shown in Table I. It can be seen that the hematocrit and plasma protein concentration showed a progressive rise in every instance except in Dog C-6 and Dog 360. In the former the hematocrit rose initially and then stabilized at about 45 in the presence of a progressive dehydration (as indicated by the plasma volume studies) and in the absence of hemorrhage. In Dog 360 the hematocrit fell terminally after an initial rise. In this dog and in Dog 359 gross and microscopic pathologic changes characteristic of shock were present.

All of these animals were permitted to eat and drink, and the magnitude of the loss of body water was found to parallel fairly well the amount and frequency of vomiting. The plasma volume after one to three days of obstruction showed a decrease varying from 9 to 46 per cent and the "available (thiocyanate) volume," or roughly the extracellular fluid volume, showed a loss varying between 5 and 30 per cent.

TABLE I

BLOOD STUDIES OF DOGS WITH PYLORIC OBSTRUCTION

Dog No.	Postoper. Day	Hematocrit Cc./100 Cc.	Plasma Chlorides M. Eq./L.	Plasma Protein Gm./100 Cc.	Plasma Volume in Cc.	Percentage Change of Volume Plasma	Percentage Change of Volume Thiocyanate	Percentage Change in Total Circulating Plasma Protein
C-1*	0	42.6	115.5	5.75	600			
	1	48.7		7.86				
	2	51.4	98.5	9.25	417	−30	−28	+12
C-2*	0	49.7	109.1	5.78	836			
	2	59.1	88.1	8.70	450	−46	−21	−19
C-3*	0	40.8	112.0	8.20	868			
	1	45.2	97.0	9.45	692	−20	−10	− 8
C-4*	0	38.0	114.1	6.24	591			
	1	44.2		7.30	538	− 9	−15	+ 7
	2	45.6	113.3	8.03	539	− 9	− 8	+17
C-5*	0	47.5	111.2	6.63	935			
	1	50.8	101.3	6.92	785	−16	− 5	−12
	2	51.8	97.2	7.97	745	−25	− 6	− 4
C-6*	0	42.4		6.86	1148			
	1/3	44.6		7.64				
	1	45.3		8.02	866	−25	− 7	−12
	2	45.2	87.9	8.71				
	3	45.3	73.6	9.23	760	−34	−11	−11
359†	0	33.2	111.2	6.43	865			
	1	46.0	103.6	7.33				
	2	50.7	99.0	8.81	630	−27	−30	0
360†	0	49.4	112.0	6.80	637			
	1/2	57.5	106.7	7.78				
	1	65.0	102.3	9.36	498	−22	−25	+ 7
	1 1/2	61.5	105.7	9.50				

*Dog killed. Autopsy showed no pathologic evidence of shock.
†Dog allowed to go on to death. Autopsy showed pathologic changes characteristic of shock.

Although the hematocrit and plasma protein concentration indicated dehydration, they did not reflect the actual loss of the plasma volume. The electrolyte loss as indicated by the chloride level in this series varied widely, but could be correlated quite well with the extent of vomiting.

TABLE II

BLOOD STUDIES OF DOGS WITH JEJUNAL OBSTRUCTION

Dog No.	Postoper. Day	Hematocrit Cc./100 Cc.	Plasma Chloride M. Eq./L.	Plasma Protein Gm./100 Cc.	Plasma Volume in Cc.	Percentage Change of Volume Plasma	Percentage Change of Volume Thiocyanate	Percentage Change in Total Circulating Plasma Protein	Remarks
316	0	43.5	110.0	5.94	565				Food and water permitted. Obstruction released after 3 days. I. V. norm. saline given (750 cc. x 2).
	1	55.8	98.1	7.78					
	2	57.0	80.1	8.40	431	−24	−16	+ 8	
	5	41.2	96.7	5.67	538	− 5	+ 1	−10	
	40	41.5	108.6	6.46	570	+ 1	0	+ 9	
42-9*	0	46.0	108.4	5.95	835				Dog took very little food and water. Died 30 hours after last studies.
	3	63.0	107.1	8.71	578	−31	−30	+ 1	
	4	61.6	108.1	8.02	795	− 5	−19	+29	
	5	63.2	110.7	7.93	710	−15	−23	+13	

*Dog allowed to go on to death. Autopsy showed pathologic changes characteristic of shock.

In Table II the findings on two dogs with high jejunal obstruction are shown. They reacted much like the dogs with pyloric obstruction, and here the rapidity of dehydration again depended largely on the amount of vom-

iting. In Dog 316 physiologic saline was given and the obstruction was released after three days, and the animal eventually showed a return to normal.

TABLE III

BLOOD STUDIES OF DEHYDRATED DOGS WITH ILEAL OBSTRUCTION

Dog No.	Postoper. Day	Hematocrit Cc./100 Cc.	Plasma Chloride M. Eq./L.	Plasma Protein Gm./100 Cc.	Plasma Volume in Cc.	Percentage Change of Volume: Plasma	Thiocyanate	Percentage Change in Total Circulating Plasma Protein	Remarks
316*	0	41.5	108.6	6.46	570				Food and water permitted but largely refused after 3 days. Low ileal obstruction.
	3	46.7	99.9	7.83	532	− 7	−15	+13	
	6	41.7	96.6	7.04	539	− 5	−22	+ 3	
	9	39.7	95.9	6.90	482	−15	−22	−10	
	12	35.9	97.0	6.61	473	−17	−23	−15	
319*	0	37.6	110.8	5.62	655				Given 500 cc. saline after blood studies on 3d day. Low ileal obstr.
	3	44.1	107.0	6.38					
	4	35.2	106.6	5.69	495	−25	−15	−23	
337*	0	44.5		6.29	637				Very little food and water permitted. High ileal obstruction.
	2	47.5	101.4	7.11					
	3	46.4	91.6	6.71	583	− 9	−15	− 2	
	4	46.1	91.9	6.92	502	−21		−13	
338†	0	46.2	112.6	5.83	850				Very little food and water permitted. High ileal obstruction.
	2	47.6	107.6	6.09	670	−21	− 8	− 8	
	4	46.1	111.7	6.02	648	−24	−16	−13	
339†	0	60.0	109.2	6.03	870				Food and water permitted. Midileal obstruction.
	3	63.2	85.0	7.65	432	−50	−18	−37	
	3 1/2	67.1	78.8	8.85					
42-10†	0	55.5	105.2	5.70	749				No food and water. Low ileal obstruction.
	2	57.0	113.4	7.05	698	− 7	− 2	+15	
	5	58.0	111.5	7.86	655	−13	−12	+21	
	2	34.4	113.4	5.97	657	−33	−24		
42-13†	4	35.7	115.6	6.55	705	−28	−27		Given no food and very little water. Dog consumed own vomitus.
	7	40.4	122.0	7.14	674	−31	−33		
	10	41.6	123.9	7.89	599	−39	−36		

*Dog killed. Autopsy showed no pathologic evidence of shock.

†Dog allowed to go on to death. Autopsy showed pathologic changes of shock.

In Table III the results are shown in seven dogs with ileal obstruction. In most instances the experimental value for the hematocrit and plasma protein concentration indicated directional changes in the plasma volume when compared with the control levels, but rarely did they indicate quantitative changes. The plasma volume again varied widely (−7 to −50 per cent) depending on the amount of food and water consumed and, thus, the associated vomiting. The plasma chloride concentration in Dogs 337 and 339 was low because of extensive vomiting and normal or high in Dogs 338, 42-10 and 42-13 in which practically no vomiting occurred. The decrease in the total circulating plasma proteins was often great, although in no instance was this discernible from the plasma protein concentration. In Dogs 316 and 42-13 vomiting was infrequent and there was little evidence of distention. In such animals, as the survival period was more prolonged, the hematocrit and plasma protein concentration were even less reliable indices of the extent of dehydration because of the effect of malnutrition.

The findings in animals with colonic obstruction are presented in Table

TABLE IV

BLOOD STUDIES OF DOGS WITH COLONIC OBSTRUCTION

Dog No.	Postoper. Day	Hematocrit Cc./100 Cc.	Plasma Chloride M. Eq./L.	Plasma Protein Gm./100 Cc.	Plasma Volume in Cc.	Percentage Change of Volume: Plasma	Thiocyanate	Percentage Change in Total Circulating Plasma Protein	Remarks
333*	0	48.7	106.0	6.66	785				Food and water permitted.
	3	50.2	97.9	7.38	750	− 4	0	+ 6	
344*	0	47.2	113.3	5.92	607				Food and water permitted. Vomiting not marked.
	3	45.9	105.3	5.58					
	5	43.2	103.1	5.41					
	8	44.3	97.4	5.66	583	− 4	− 9	− 8	
	11	40.8	94.3	5.31	526	−13	− 7	−22	
	12	45.1	102.0	5.58					
315†	0	51.6	103.6	6.76	812				Food and water permitted. Vomited last 6 days and refused feedings.
	2	53.3	98.4	6.73					
	5	50.7	97.2	6.40					
	8	54.2	87.5	6.53	640	−21	−13	−24	
	10	53.0	81.6	6.49	618	−24	− 8	−27	
	13	52.5	80.9	8.04	445	−45	−27	−35	
42-7†	0	47.6	105.2	6.58	600				Dog permitted food and water.
	3	51.0	97.4	7.32	578	− 4	0	+ 7	
	7	50.0	93.7	6.21	568	− 5	−12	−12	
	10	53.8	86.8	6.03	558	− 7	−12	−15	
	14	55.2	77.5	5.37	392	−35	−15	−47	

*Dog killed. Autopsy showed no pathologic evidence of shock.

†Dog allowed to go on to death. Autopsy showed pathologic changes characteristic of shock.

IV. In this series it can be seen that the hematocrit and plasma protein concentration are not reliable indices of the plasma volume change owing largely to the effect of malnutrition. The extent of malnutrition in such animals can be best evaluated by the decrease in the total circulating plasma proteins (column 9). The fall in the plasma chloride level can be seen to be quite marked, especially in the last two dogs in this series, in which vomiting during the last five to seven days of life was quite extensive.

These animals were permitted to have food and water which they ingested freely for six or seven days. Vomiting was rare during the first week of illness and during this time the plasma volume studies showed little change. During the second week, the loss of fluids and electrolytes was more marked, and apparently because of this and also because of a diminished intake there was a precipitous fall in the body water. The plasma volume changes can be seen to vary from −4 per cent to −45 per cent and the "available (thiocyanate) fluid" volume from 0 per cent to −27 per cent.

Because of the associated malnutrition in this colonic series, it was decided to study animals that did not have intestinal obstruction but from which food and water were withheld, thus evaluating the effects of starvation. The results on four such animals are shown in Table V. The plasma volume showed decreases of from 15 to 30 per cent in from three to seven days, and the "available (thiocyanate) fluid" decreased from 4 to 20 per cent.

The hematocrit and plasma protein concentration again did not reflect the plasma volume loss in a quantitative manner; in fact, the experimental

TABLE V

BLOOD STUDIES OF DOGS FROM WHICH FOOD AND WATER WERE WITHHELD

Dog No.	Days of Starvation	Hematocrit Cc./100 Cc.	Plasma Chloride M. Eq./L.	Plasma Protein Gm./100 Cc.	Plasma Volume in Cc.	Percentage Change of Volume Plasma	Percentage Change of Volume Thiocyanate	Percentage Change in Total Circulating Plasma Proteins
359	0	31.9	111.8	6.20	865			
	3	33.8	111.0	6.53	737	−15	−16	−10
	4	33.7	111.5	6.37				
358	0	36.7	110.2	6.02	647			
	2	39.6	110.8	6.25				
	4	40.1	111.8	6.07	528	−18	− 4	−18
352	0	49.2	106.0	7.14	713			
	6	55.5	113.0	6.99	498	−30	−15	−32
	8	50.0	110.0	6.15				
338	0	42.1	114.6	5.81	850			
	5	51.4	121.4	6.36				
	7	52.9	121.2	6.41	600	−29	−20	−22

values were frequently about the same as the control levels. The loss in total circulating plasma proteins due solely to malnutrition was great (10 to 32 per cent). The plasma chloride levels were normal or slightly high, and yet because of the diminished extracellular fluid volume the total body electrolytes were lower following the period of starvation than in the control period.

COMMENT.—It seems pertinent, first of all, to enumerate the possible ways in which body water in intestinal obstruction might be diminished. Probably the most frequent cause for reduction is a diminished or inadequate fluid intake. As shown by the experimental work represented in Table V, animals which receive inadequate amounts of food and water may show decreases in body fluids which are great. This must also occur frequently in human patients to a varying degree. During the starvation, or reduced intake period, the elimination of body water continues, and, although the amount might be diminished, fluid is lost through the lungs, sweat glands and kidneys.

The second most frequently seen cause for a reduction of body water is abnormal losses. In cases of intestinal obstruction this occurs largely owing to vomiting. As Peters[7] has repeatedly pointed out, the amount of vomiting is largely dependent on the intake of food and liquid. When fever is present, the loss due to sweating might be quite significant, and, occasionally, when the obstruction is partial, diarrhea may occur and contribute to the fluid loss. Naturally, gastro-intestinal secretions which accumulate above the point of obstruction or are removed by intestinal intubation might be considerable and frequently constitute as great a loss, if not greater, than fluid which is lost during emesis.

The diminution in body water by the two processes (decreased intake and increased output) thus may result in great decreases in plasma and interstitial water. The deficit of plasma proteins results largely from an insufficient caloric and nitrogen intake and an associated break-down of tissue proteins. Animals,[8] and patients,[9, 10] have been shown to be in a rather marked degree of negative nitrogen balance, especially during the early

periods of starvation, and when fever and infection are present. The change in the amount of total circulating plasma protein thus must depend largely on the degree of reduction in the nitrogen intake, the rate of destruction of plasma and other tissue proteins, and the reserve stores present at the onset of illness. The electrolyte loss may also be of considerable importance. If vomiting occurs or gastro-intestinal drainage is instituted, a significant decrease in the body electrolytes may result. As has been previously pointed out, such an electrolyte loss may lead to severe alkalosis if gastric secretions are lost, or to acidosis if duodenal fluid is lost, and thus cause a shift of fluid from the plasma and interstitial spaces where it is greatly needed into the intracellular compartments.[13] When sodium is lost from the body, the plasma and the interstitial fluids are temporarily in an hypotonic state. To restore equilibrium two mechanisms operate: First, urine is excreted which has a low concentration of electrolytes; and, secondly, water passes from the extracellular phase into the intracellular compartment. Thus, when a primary electrolyte loss occurs, a diminution in the extracellular volume may occur due both to water loss in the urine and a water shift into the tissue cells.[13]

It should be stressed that the degree of body water loss can rarely be estimated from the plasma chloride concentration. In the various types of intestinal obstruction studied in this series at least one animal in each group (pyloric, jejunal, ileal and colonic) showed severe electrolyte loss as demonstrated by the plasma chloride concentration. However, as McIver and Gamble[15] pointed out, in 1928, the loss of bile and intestinal fluid containing approximately the same amount of fixed base (sodium) and chloride as does plasma may occur. Such a loss will produce a reduction in the total amount of body electrolytes and a diminution in the plasma and interstitial fluid without altering the plasma chloride or bicarbonate concentrations. Thus, in some of the animals reported, a reduction of fluid and electrolytes occurred even though the plasma concentrations were high or normal. For example, Dogs 42-9 (Table II) and 42-13 (Table III) had extracellular fluid volume losses amounting to about one-third of their volume, and without any electrolyte loss one would expect a rise in the plasma chloride level to around 150 M. Eq. per liter. This does not occur normally because of the ability of the kidneys to excrete the excessive electrolytes and thus maintain the body fluid in an isotonic state and preserve a normal acid-base balance. However, when dehydration becomes severe, the body cannot supply adequate amounts of water for the formation of urine, or if kidney damage intervenes prior to this, a rise in the blood nitrogenous products, in the plasma chloride concentrations, and even occasionally in the total base (sodium or bicarbonate) occurs.

Besser,[16] in 1940, reviewed the literature on intestinal obstruction, and summarized an earlier paper by Elman and Hartmann,[17] in which they stated that low (ileocecal) obstruction in only rare instances caused death by changes in body fluids which resulted in circulatory and renal insufficiency

due to dehydration. Such work assumed that the extent of body fluids was unaltered because the concentrations of various blood constituents remained normal. As pointed out above, the blood chemistry may be normal even though dehydration is severe. The actual extent of electrolyte loss or gain can be estimated only by determining the total loss of circulating plasma chloride and interstitial fluid chloride levels and not by the changes in the plasma concentration.

The third cause for a reduction in the plasma volume is distention of the gastro-intestinal tract. As Gendel and Fine[18] have shown, the loss of plasma might be great and might account for death *per se*. Gatch and Battersby[19] have also pointed out that the loss might be large by this avenue and the damage to the vascular bed might be irreversible so that even with relief of the distention body water continues to be lost.

Aird,[20] using the vital red method for determining the plasma volume, states that the blood volume in some experimental animals with intestinal obstruction is depleted before death but says "this occurs only when intestinal distention is extreme." This view is not entirely in keeping with our data for several reasons: First, many of the animals reported in this paper, which showed moderate to large reductions in their plasma volume, were killed after the determinations were made, and autopsy showed little evidence of distention. Secondly, the results obtained in the animals which were not permitted to have food and water showed that the plasma volumes could be decreased significantly (30 per cent) without vomiting or distention being present. Therefore, it would appear that while distention is an important factor and may cause a rapid loss of plasma, the same may occur over a longer period in its absence.

Fine and Gendel[21] also have stated "that when, and if dechlorination occurs in the course of intestinal obstruction it is by no means a crucial factor in the lethal effects of obstruction." In another publication[22] they stated that "as the plasma volume falls the hematocrit rises. This increase in hematocrit is far greater than can be explained by dehydration, however severe." They also concluded that dehydration and electrolyte imbalance are not responsible for the greater part of the plasma loss.

This was undoubtedly true in their series, but it should be remembered that they studied intestinal distention *per se* over a period of hours rather than days, and that the effects of dehydration as seen in our animals could not be found in short-term experiments. Granted that distention alone can produce large alterations in the plasma volume and that it might often be the most important factor, it should also be borne in mind that just as great alterations in the plasma volume in intestinal obstruction can occur in its absence, due solely to dehydration and can also lead to just as serious results.

To lend further support to this view, Davis[23] has shown that by the injection of 25 per cent salt solution subcutaneously, all the pathologic findings of shock might be produced. Several such experiments were repeated

by us, and in each instance there was a marked progressive rise in the hematocrit and plasma protein concentration and, immediately after death, autopsy revealed the pathologic findings of shock. These animals showed various side-effects which are usually not seen in shock, such as twitchings of all extremities, even to the point of convulsions, and extremely high temperatures (rectal temperature in one animal, taken repeatedly for several hours prior to death, varied from 43° to 44.5°C.). On the other hand, dehydration produced by injecting 5 per cent glucose in distilled water (100 to 200 cc. per kilogram of weight) intraperitoneally, as described originally by Darrow and Yannet,[24, 25] will produce a marked lowering in the plasma volume.[13] If the animals are dehydrated sufficiently, all the pathologic changes of shock are present at death. These animals show the signs and symptoms characteristic of shock (cold extremities with a low temperature and hemoconcentration with a diminishing plasma volume).

The fourth factor which might lead to a diminution of the effective blood volume in intestinal obstruction occurs when strangulation of a loop of intestine takes place. Unpublished data,[26] from this laboratory, showed hemorrhage to occur into the intestine of several such animals, although occlusion of the blood supply to the obstructed loop was produced in each instance. Also serosanguineous peritoneal fluid was present. Factors which have been enumerated above (starvation, vomiting, and distention) undoubtedly also occur in patients when a loop of bowel becomes incarcerated or strangulated. In human patients an even greater difference might be encountered than is seen in the experimental animal, probably because of the wide variation in the degree and duration of strangulation or incarceration, and also because of differences in the degree of early vascular impairment. Gatch and Culbertson[27] have shown that the blood supply to a distended loop will be impaired if the distention is great enough. On the other hand, in patients the vascular supply might possibly be greatly reduced prior to the time distention occurs (volvulus or herniation of a loop). Thus, in strangulation, impairment to the blood supply of the affected loop undoubtedly occurs if the condition progresses far enough. It might take place early in some cases (mesenteric vessels occluded) or later in others (when distention takes place and the smaller vessels in the bowel wall are affected). When the mesenteric vessels are involved, hemorrhage may occur either into the obstructed loop or above or below it. Thus hemorrhage might occasionally be an additional factor in reducing the volume of circulating blood.

An attempt should be made to try to differentiate between a loss of plasma water and a loss of plasma protein. In starvation and vomiting there is initially just a loss of fluids and electrolytes. Malnutrition and an increased rate of catabolism (due to fever, infection, *etc.*) may reduce the body proteins and then, terminally, when the circulation is greatly impaired, there might also be an actual loss of protein through the capillary walls. Gatch and Battersby[19] have shown that in gastro-intestinal dis-

tention, plasma water and proteins are lost, and certainly this also occurs in strangulation with or without hemorrhage. In a recent publication, Bowers[28] pointed out the degree of plasma protein loss which might occur in experimental appendicitis with peritonitis. While it has been known for some time that protein is lost with the formation of sterile or infected exudations, this possibility should also be kept in mind in intestinal obstruction. In several animals, which were not included in this series, because a second operation was performed to relieve the obstruction, purulent fluid, which contained a large amount of protein, was found in the peritoneal cavity at autopsy. Thus, in the presence of infection or gangrene in cases of intestinal obstruction, plasma water and proteins might decrease quite markedly. The severity of the symptoms or the rapidity of death from intestinal obstruction, therefore, depends on the number of factors which enter into the picture. In this paper the cause of death due to absorption of so-called toxic products has not been dealt with. While it is conceivable that such products might possibly exist, and even produce serious effects, it is believed that sufficient evidence has been presented to show that death can occur in intestinal obstruction at various levels purely from an excessive loss of body water and, hence, impairment to the vascular system (with or without renal dysfunction).

In the animals reported, wide variations in the hematocrit, protein concentration, and total circulating plasma protein levels occurred. Because of this, as has been previously stated elsewhere,[10, 29 and 29a] it is believed that in most instances the hematocrit and plasma protein concentration, while they might show directional changes, cannot be employed to estimate quantitatively alterations in the plasma volume. It has been shown that the longer the period of malnutrition, the more inaccurate these levels become.

Many of the results in these animals were included in a previous publication[29] to lend support to the theory that contrary to the previous belief,[30, 31] the plasma volume is not maintained initially at the expense of the interstitial fluid, and, thus, alterations in the hematocrit and protein concentration might be indicative of early as well as late changes.

In the treatment of intestinal obstruction all factors should be kept in mind. If this be done, and treatment is carried out accordingly, the mortality rate would then largely depend on whether or not irreversible changes had occurred (severe distention, gangrene or infection). In the event large amounts of plasma proteins are lost, it is easy to see why physiologic saline alone is of little value in restoring body fluids. It has been suggested that, because saline would not greatly prolong life in low intestinal obstruction, there was little electrolyte and fluid imbalance in such cases. This is obviously not true, unless exact replacements of saline, plasma, and whole blood were carried out daily and their rapid loss (due to infection, distention or hemorrhage) prevented. Then, in the event that death occurred and autopsy showed the typical pathologic findings, such a statement would be possible.

The gross and microscopic examination at autopsy showed the same pathologic findings in the animals which went to death as those described by Moon and Morgan[32] (hemorrhagic changes in the lungs, submucosal intestinal hemorrhages, *etc.*). In no instance were such findings seen in the animals killed prior to death even though in some cases dehydration was severe. Such pathologic changes must, therefore, occur as a terminal event.

SUMMARY

The reduction of body water in intestinal obstruction might occur in one or more of the following ways:

1. Reduced intake.
2. Excessive loss (or normal loss and restricted intake).
   a. Vomiting.
   b. Perspiration.
   c. Urinary.
   d. Diarrhea.
3. Distention.
4. Strangulation.
   a. With or without hemorrhage.
   b. Transudation of fluid.
5. Infection.
   a. Exudation of fluid.

Any one of the aforementioned items may cause death due to a peripheral vascular collapse, if allowed to progress for sufficient time, but more commonly in intestinal obstruction at least two or more are present.

A decrease in the body protein might result owing to:

1. Reduced intake of food.
2. Excessive destruction.
3. A loss of whole blood or plasma from the vascular system.

Because of such decreases, the hematocrit and protein concentration cannot be employed to estimate quantitatively the reduction in the plasma volume.

The wide variation in the signs, symptoms and course of clinical cases depends on the severity and number of the previously mentioned factors, and the degree and type of treatment. Success in treating patients would, therefore, depend on the recognition of the causes of loss of body water that exist and the restoration of these to normal (the correction of fluid and electrolyte balance and the replacement of the plasma protein loss). This cannot be accomplished if distention, vascular damage and infection cannot be corrected. Thus, it is evident that physiologic saline, plasma, or whole blood will continue to leak out of the vascular system unless the cause for the loss can be removed.

CONCLUSIONS

1. Evidence has been presented to show that dehydration resulting from intestinal obstruction (pyloric, jejunal, ileal or colonic) may be severe enough to cause death in itself if the condition exists for a sufficient time.

2. The amount of gastro-intestinal fluid lost varies greatly, depending on the level and degree of obstruction, and the amount and frequency of vomiting. The body water deficit, usually resulting from a diminished intake and an excessive loss, may be greatly accelerated when distention, strangulation, hemorrhage or infection occurs.

3. The rapidity of body water loss depends on the number of causes present and the severity of each. This explains the wide variation seen in the course of the disease in patients with intestinal obstruction.

4. The success of the treatment depends largely on the completeness with which the body water can be restored and on the prevention of further losses.

5. The hematocrit, plasma protein level, and the plasma chloride concentration cannot be employed to estimate quantitatively the decrease in the plasma volume.

6. The deficit in total circulating plasma proteins might be considerable in cases of intestinal obstruction, especially in those cases of long duration, and this loss is usually masked by hemoconcentration, and, thus, cannot be recognized by the plasma protein concentration.

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A STUDY OF PLASMA PROTEIN VARIATIONS IN SURGICAL PATIENTS

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WHIPPLE[1] has recently stated: "It is our belief that the plasma proteins take an active part in the internal protein metabolism of the body, that they are built up rapidly, used in the body economy freely, and serve to supply practically all of the protein requirements of the cells of the body." The importance of hypoproteinemia in surgical patients has been stressed repeatedly.[2, 3, 4] It is well known that many complications may develop in the postoperative period as a result of hypoproteinemia and that these may be prevented frequently by adequate prophylactic and therapeutic measures. We have previously pointed out that the fundamental causes of this deficiency state may not be known definitely although the liver has a rôle of great importance in maintaining an adequate level of the plasma proteins. However, there are many factors associated with, or related to, operative procedures which have a profound effect on the concentration of the plasma proteins. The presence of low plasma protein concentrations should be taken as an indication of a profound nutritional disturbance and the local manifestations, while important in themselves, assume greater importance as an indication of depletion of the reserve stores of protein and a general metabolic disturbance. These changes render the patient especially susceptible to infections and toxins. The present study is an attempt to determine: (1) The incidence of hypoproteinemia associated with operations, and the relationship to various procedures; (2) the factors which influence changes in plasma proteins; (3) the relationship between liver disorders and hypoproteinemia; and (4) methods of preventing and treating hypoproteinemia.

METHODS OF STUDY

A series of 215 surgical patients have been included in this study. These cases were selected from the surgical services of the Hospital for Joint Diseases as they were admitted, no attempt being made to segregate or select specific cases. Preoperative determinations of the total plasma proteins and hematocrit were made on every patient in addition to other blood chemical studies which were done when indicated. Blood specimens were taken postoperatively at 12- or 24-hour periods depending upon the nature of the case, and these specimens were examined for total plasma protein and hematocrit reading. The specimens, when practicable, were drawn early in the morning and no blood was taken while intravenous fluid was being

administered, except in emergencies. As a rule, parenteral fluids had been discontinued for at least two to four hours before the blood was withdrawn. Occasionally it was not possible to discontinue the administration of fluid. In these cases the rate of administration was slowed as far as possible and the blood drawn from the opposite arm. Fluid at all times was administered in volume and amounts calculated to maintain or restore normal fluid and electrolyte balance. The blood samples were drawn into Sanford-Magath hematocrit tubes containing 1 mg. of heparin. The technic of Scudder,[35] as outlined in his monograph on blood studies in shock, was followed in detail. The hematocrit tubes were centrifuged for one hour at 2500 revolutions per minute and the hematocrit read. The supernatant plasma was then used for determination of the total plasma protein, using the falling-drop method (Hamilton, Barbour apparatus). Three determinations were carried out on each sample and if a variation of over 0.2 Gm. was observed, the sample was discarded and the entire procedure repeated. This method was selected because of the rapidity of determination which it makes possible. While this does not give the protein fractions, it serves as an adequate guide in surgical cases, inasmuch as the albumin fraction is usually the variant and the globulin fraction varies little and is of slight significance from a surgical viewpoint.

The importance of plasma volume determinations particularly in the estimation of protein reserve is well recognized, but we have not carried out these studies because the procedures are time-consuming and not well adapted to clinical routine. We feel that frequent determinations of blood concentration and plasma proteins afford sufficient check for routine use. The significance of increasing hemoconcentration (as indicated by an elevated hematocrit reading) is well recognized as diagnostic of certain type of shock, dehydration, and decreased blood volume, but the equal importance of diminished blood concentration should not be overlooked. This may be associated with shock, as well as with hemorrhage and may also indicate decreasing circulating blood volume. Careful attention to the results of the hematocrit and plasma protein determination is sufficient, we feel, to act as a guide for therapy.

In addition, in a selected group of patients, determinations of liver function were made by the hippuric acid excretion test.[5] This is performed as follows: The fasting patient is given 1.77 Gm. of sodium benzoate in 20 cc. of distilled water intravenously after having emptied the bladder. Two glasses of water (500 cc.) are given to the patient and the urine collected in exactly one hour, catheterization being employed if necessary. The content of hippuric acid in the urine is determined by the Quick method. Values of one gram or over are considered normal. We have used this test on several hundred patients and feel that it is probably the best single test for determination of liver function. This is particularly true in the non-jaundiced patient and in those with mild degrees of liver damage such as may be found associated with chronic gallbladder disease or thyrotoxicosis.

Many others have testified to the value of the hippuric acid test in determining the ability of the liver to withstand operative procedures.[6, 7, 8] This function test measures the ability of the liver to synthesize amino-acetic acid. This is a very delicate function and one for which the liver has little or no reserve. It, therefore, enables us to detect very slight alterations in liver physiology.

Following the operative procedures, determinations of plasma proteins and hematocrit were made immediately and at intervals of 12 to 24 hours until the patient had completely recovered. The determinations were repeated for this period because it was noted that many cases developed a secondary or delayed drop after having once returned to normal.

TYPE OF OPERATIONS

There are many factors which influence the level of the plasma proteins and it is obvious that there will be different degrees of variation as a result of different operations. Among the immediate causes of plasma protein depletion are operative shock and blood loss. Other causes not so immediately apparent are: The previous nutritional state of the patient and the protein reserve; the degree, if any, of liver damage; and the effect of anesthesia, which may operate through its effect on the blood volume directly or on the liver.

Coller,[9] and others, have shown that blood loss under ordinary circumstances varies according to type of operation. The amount of blood lost during a hernioplasty or appendicectomy may be no more than 100 cc., while during a radical breast amputation it may total 1000 cc. Similarly, degrees of operative shock may vary. Handling of intestines may cause a marked degree of plasma loss from the vascular channels, and operations on bones or extremities may cause a similar loss. These two factors, blood loss and shock, will cause an immediate loss of plasma proteins and a decrease in the protein level of the plasma. Since most patients have a large reserve of proteins for plasma protein regeneration the deficit will soon be corrected if, indeed, in the interval it has not been restored by whole blood or plasma transfusions. In patients who come to operation in a poor nutritional state as a result of vomiting, diarrhea, dietary restrictions, or other causes, the reserve proteins may have been depleted. In addition, this malnutrition may have affected the liver so that the synthesis of stored protein into plasma protein is impaired, and the result will be prolonged low levels of plasma proteins.

In order to evaluate properly the results obtained in this study, the figures were subjected to a careful statistical analysis. It is well known that the larger the group of patients under consideration, the more significant will be the results. The significance of a given set of figures is usually determined by the calculation of the standard error and the relative deviate. This standard error is commonly designated by σ (sigma), and is a measure of the amount that a given percentage could vary due to experimental error

or chance alone. In Table I, this column of figures is based on the percentage of cases showing a fall in proteins for the whole group and the size of each particular group.

The relative deviate is the ratio of x to σ, where x is the difference between the percentage observed for a particular group and the overall percentage for all groups, and σ is the standard error. It is common statistical practice to take a relative deviate of 2.5 as the limit of significance because this represents the point beyond which an observed percentage could be expected to be only one per cent of the time, or once in a hundred similar experiments, due to chance alone. When an observation is such that it could be expected to be due to chance only once in 100 experiments the inference is that it is not the result of chance variation but that it is the result of a set of characteristics or conditions which make the group under consideration different from the other groups or from the average of the other groups combined. This is what is meant by a significant difference.

TABLE I

INCIDENCE OF POSTOPERATIVE DECLINES IN PLASMA PROTEINS IN VARIOUS TYPES OF OPERATION

Type of Operation	No. of Cases	Cases with Fall in Proteins: No. of Cases	Per Cent	Standard Error (σ)	Relative Deviate (x/σ)
1. Appendicectomy for acute appendicitis	23	16	69.6	9.65	0.07
2. Cholecystectomy for cholecystitis or cholelithiasis	27	22	81.5	8.91	1.41
3. Major procedure on the gastro-intestinal tract	26	26	100.0	9.07	3.43
4. Operations for acute abdominal emergencies	19	15	79.0	10.62	0.95
5. Hernioplasty for inguinal hernia	18	4	22.2	10.91	4.28
6. Orthopedic operations	34	24	70.6	7.93	0.21
7. Thyroidectomy for Graves' disease	17	12	70.6	11.23	0.15
8. Gynecologic operations	29	18	62.1	8.59	0.79
9. Miscellaneous operations	22	11	50.0	9.87	1.91
Totals	215	148	68.9	3.16	

On the basis of the foregoing, the results of a series of 215 cases were analyzed (Table I). Of these 148 patients (68.9 per cent) showed a significant fall (more than 0.5 Gm.) in their plasma proteins following operation. A standard error of 3.16 per cent indicates that the observed percentage could be expected to vary so that in repeated experiments with groups of 215 patients in only 95 experiments out of 100 it might be expected to be between 62.6 and 75.2 per cent. This statement is based on the following assumptions:

(1) That the cases represent a random sample of the conditions under discussion. No attempt was made to select particular patients and the cases were studied essentially in the order in which they were admitted to the surgical wards.

(2) That a fall in plasma proteins is an objective observation which is not subject to varying interpretation by different observers. No fall in protein was included unless it exceeded 0.5 Gm. Each blood sample was subjected to three plasma protein determinations and if the difference was greater than 0.2 Gm. the sample was discarded and another blood specimen drawn.

(3) That the figure of 68.9 per cent represents the average of the various percentages which would be obtained in repeated experiments. While this is not necessarily true it is accepted because it is impossible to make a better assumption.

In many of the patients the declines occurred despite blood or plasma transfusions at the time of operation. Occasionally the fall in proteins was to a subnormal level but more frequently the plasma protein level was considered normal, although from 1 to 2 Gm. below the preoperative level. A concomitant decrease in the hematocrit reading was frequently observed, particularly in those patients in whom the amount of blood lost at operation was excessive. Insofar as possible, this was corrected by appropriate fluid therapy.

Of the nine different types of operations performed upon these 215 cases, only the group of major gastro-intestinal operations showed a significantly higher incidence of protein loss than the group as a whole. The series of 26 cases is certainly large enough to indicate that a fall in protein will occur in operations of this type more frequently than in other operations, although from a statistical point of view it is not possible to state that this fall must occur in every major gastro-intestinal procedure.

The importance of these findings is obvious. Patients in this category have frequently suffered depletion of their reserve stores of protein prior to operation. Add to this a high incidence of significant protein loss as a result of operation, and a true hypoproteinemia frequently ensues. The clinical complications resulting from this state invariably contribute to a prolonged morbidity and an increased mortality.

At the other extreme, hernioplasty showed an incidence of protein fall significantly different from the total group (relative deviate 4.28). In these cases we can expect a decidedly lower frequency of diminished protein levels.

Cholecystectomy and operations for acute abdominal emergencies showed a higher percentage than the average (81.5 and 79.0 per cent, respectively). However, the relative deviates in these groups are below 2.5 and, therefore, it is not possible, statistically, to say that figures approaching these percentages would be found in all similar groups of cases. Obviously a larger series must be studied. Further information can be obtained by correlating these figures with those of liver function (Table II). This will be discussed subsequently.

It is in these groups, in which the relative deviate approaches but does not reach a level that can be considered truly significant, that clinical judgment must be exercised carefully. In acute abdominal emergencies, the added factor of shock is so frequent that this group deserves the most careful preoperative and postoperative care. In patients undergoing cholecystectomy the status of the liver, not uncommonly damaged as a result of prolonged gallbladder disease, must be accurately ascertained.

In all groups when the relative deviate is less than 2.5 the indication is

merely that for the size of the group the difference in percentage is not sufficiently large to be called significant. For example, considering the group of cholecystectomies, if the same percentage were to be found in a group of 85 similar cases rather than in 27 cases, the difference would be significant. Further studies are being conducted along these lines at the present time.

One must realize that statistical evaluation is valueless without clinical judgment and a thorough appraisal of the patient. Many factors resulting from the nature of the disease and the operative procedure, as well as from the nutritional status of the patient, must be considered in attempting to prognosticate the changes in the plasma proteins. For example, a patient undergoing cholecystectomy or thyroidectomy in whom the various liver

TABLE II

SUMMARY OF CASES INCLUDED IN THIS STUDY

Type of Operation	No. of Cases	Total No. of Cases	No. of Cases with Fall in Proteins	No. of Cases without Fall in Proteins
1. Appendicectomy for acute appendicitis:		23	16	7
Nonperforated	17			
Perforated	6			
2. Cholecystectomy for cholecystitis or cholelithiasis		27	22	5
3. Major procedure on the gastro-intestinal tract:		26	26	0
Gastro-enterostomy	8			
Gastrectomy	6			
Intestinal anastamosis and enterostomy	4			
Intestinal resection for carcinoma	4			
Choledochostomy	3			
Cholecystogastrostomy	1			
4. Operations for acute abdominal emergencies:		19	15	4
Ruptured peptic ulcer	4			
Intestinal obstruction (gallstone)	1			
Acute pancreatitis	3			
Ruptured abdominal viscus	1			
Strangulated hernia	2			
Evisceration	1			
Pelvic abscess	1			
Subphrenic abscess	2			
Celiotomy for peritonitis	4			
5. Hernioplasty for inguinal hernia		18	4	14
6. Arthopedic operations:		34	24	10
Arthrodesis	8			
Tendon operation	6			
Arthrotomy	3			
Spine fusion	10			
Open reduction of fracture	1			
Osteotomy and bone resection	6			
7. Thyroidectomy for Graves' disease		17	12	5
8. Gynecologic operations:		29	18	11
Vaginal plastics	12			
Hysterectomy	11			
Salpingo-oophorectomy for carcinoma and abscess	6			
9. Miscellaneous operations:		22	11	11
Closure of colostomy stoma	2			
Prostatectomy (1st & 2nd stage)	5			
Resection of hypogastric plexus	1			
Tumor of abdominal wall	1			
Hemithyroidectomy for nontoxic goiter	7			
Excision of thyroglossal cyst	2			
Excision of parathyroid adenoma	1			
Radical mastectomy	3			
Totals		215	148	67

function tests reveal deficient liver activity must be expected to develop a sustained plasma protein deficit more often than one whose liver function is adequate.

When a patient is debilitated as a result of the disease process, partial or complete intestinal or pyloric obstruction, prolonged dietary restrictions, draining biliary or intestinal fistulae, diarrhea or prolonged suppuration, this factor must be carefully evaluated.

In other words, one must apply the statistical information obtained from these studies with due consideration of each patient as an individual problem.

In Table II the various cases which made up the total are listed. This is included merely to indicate the type of case which more frequently suffered from loss of proteins, but no one group is large enough for statistical analysis.

These studies are being extended now by the authors in a series of operations on laboratory animals. In dogs, for example, many factors are controllable which in the patient are subject to unpredictable variations. An attempt is being made to control the nutritional status, measure adequately the blood loss, control the nitrogen balance, and maintain blood concentration at a fairly constant level. We feel that these studies will supply further information unobtainable from the study of surgical patients.

In general, it can be said that the occurrence and extent of plasma protein depletion following operations depend upon the interrelationship of various factors. Poor nutrition, poor liver function, severe anemia, shock, hemorrhage, and prolonged operations, unfavorably influence the plasma proteins. Patients in good condition, undergoing operations such as herniorrhaphy which are complicated by none of these factors, rarely exhibit any change in their proteins.

The duration of the diminished concentration of proteins depends on many factors. Some of these will be discussed subsequently (liver factor and amount of protein reserve). As a rule, the diminution was transitory and return to normal occurred within three or four days. Other cases showed prolonged low levels and intensive therapy was essential to restore the normal concentration. When the loss of plasma protein was due to blood loss or shock, the deficit was quickly restored, but when other factors came into play, the time was prolonged proportionate to the extent of the operating factors (see case reports).

THE RÔLE OF BLOOD LOSS AND SHOCK

Every operative procedure is associated with some degree of blood loss. Usually this is insignificant, and even when fairly large amounts are lost, the deficit is quickly overcome. It seems apparent that a single hemorrhage of less than 500 cc. can be quickly compensated for and cause little or no change in the concentration of plasma proteins. Operative shock, on the other hand, resulting as it does, in diminished circulating blood volume and usually in hemoconcentration does cause alterations in the plasma proteins. A combination of both factors is responsible in most cases for a drop in the

plasma protein concentration of from 0.5 to 1.0 Gm. in the immediate postoperative period. This loss is quickly restored by the body in normal circumstances unless shock is severe or hemorrhage marked. When, however, the protein reserve has been depleted or the liver is damaged, restoration is delayed or absent and intensive therapy must be instituted.

RELATION OF ANESTHESIA TO CHANGES IN PLASMA PROTEIN

It is difficult to analyze the effect of one factor out of many on the plasma protein levels. Long operations requiring large amounts of anesthetic agents are also associated very frequently with excessive blood loss and some degree of shock, and these factors cannot be adequately segregated. However, it was observed that a definite relationship exists between the duration of anesthesia and changes in the proteins (Chart I). This correlation is very definite, as shown in Chart I, but it might be better to compare the duration

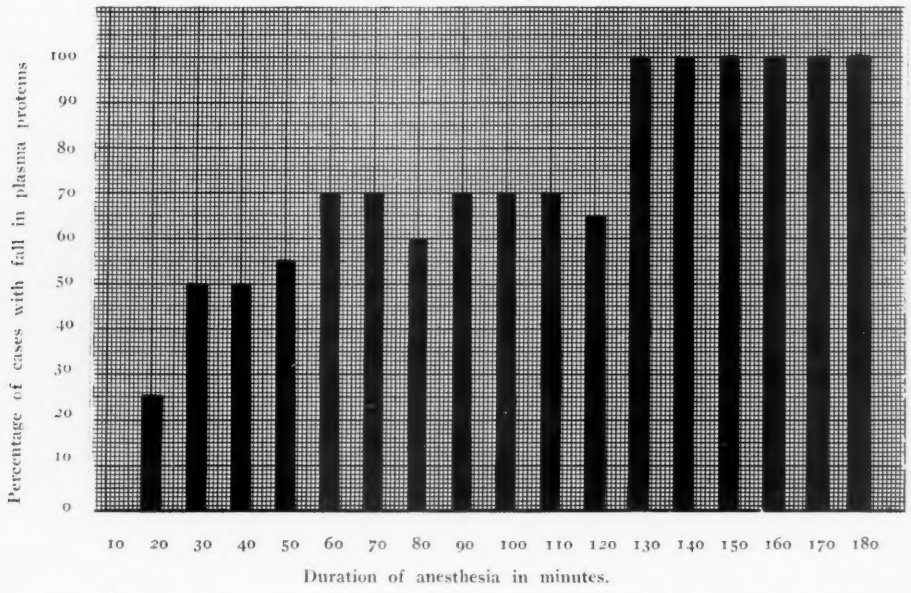

CHART I.—Relationship between duration of anesthesia and incidence of plasma protein decline.

of operation rather than duration of anesthesia, to the incidence of protein decrease. In operations under one hour, from 50 to 60 per cent of patients showed a decrease in plasma proteins, while in operations lasting over two hours, all cases showed significant falls. These figures are interesting, but an analysis of the various anesthetic agents employed in these cases, in an attempt to correlate the effect of various types of anesthesia with falls in plasma proteins, showed no significant variations.

The effect of anesthetic agents on the liver and on blood volume has been repeatedly studied. Ether, chloroform and cyclopropane are definitely toxic to the liver in certain concentrations. Likewise, they cause diminution in blood volume, principally in the plasma constituent. Procaine, used for

induction of spinal or local anesthesia, is excreted through the liver and may also have a deleterious result.[10] The effect of these actions on the level of the plasma protein would seem, theoretically, to be detrimental, but as yet we have no definite clinical evidence.

THE RÔLE OF THE LIVER

There is a large amount of experimental and clinical evidence to implicate the liver as the source of new plasma proteins. Whipple, as the result of extensive research, feels that the liver is of primary importance in the synthesis of albumin and possibly of globulin, and other workers in the field have corroborated these findings. Exact experimental proof is difficult. Animals subjected to hepatectomy exhibit profound general disturbances and die, but in these animals the albumin fraction of the plasma proteins is usually depleted. Indirect experimental evidence, however, is more convincing and has been reviewed in detail elsewhere.[2] Clinically, plasma protein depletion has been observed repeatedly in liver disease. We have observed marked declines in the concentration of the plasma proteins in patients with cirrhosis of the liver, acute yellow atrophy, and diffuse primary carcinoma of the liver. Johansen,[11] Thompson, McQuarrie and Bell,[12] and others, have made similar observations.

Moreover, control of the storage of protein reserves in the body is probably a function of the liver. There is no questioning the fact that large protein reserves are normally present in the body and that these reserve stores are also present outside the liver. The protein is stored in large aggregates and not as amino-acids. Dogs subjected to repeated plasmapheresis show prolonged ability to regenerate plasma proteins even on a protein-free diet. Elman[13] noticed a prompt response in plasma protein regeneration in dogs following bleeding. In the human, plasma protein regeneration is also observed to a similar degree. Kerr, Hurwitz and Whipple,[14] Smith, Belt and Whipple,[15] and Cutting and Cutter,[16] noticed a regeneration of 40 to 60 per cent of the circulating protein following plasmapheresis. Evidence is available to indicate that sufficient reserve stores of proteins are available to form plasma proteins equal or greater in amount to that present in the circulating blood. This reserve store is in the form of "labile" protein which is readily available for use. In addition protein is also present in the form of the dispensable reserve which is less readily available, and the fixed protein of the body cell which is never available for plasma protein formation.

It is apparent that these essential protein regulating functions of the liver depend upon good liver function. It is equally apparent that many patients admitted to the surgical wards already have deficiencies in liver function or are so-called "liver weaklings" whose liver function is sufficient for the ordinary wear and tear of existence but insufficient to cope with the added stress and strain of illness and operation. Patients exhibit subnormal liver function upon admission as a result of many factors. Malnutrition over

a long period of time as a result of diet, deficient absorption of nutritive elements of food, vomiting or diarrhea unquestionably affect the liver deleteriously. Weech[17] has stressed the importance of malnutrition. Furthermore, the nature of the disease may affect the liver. This is particularly true in diseases of the gallbladder and the bile ducts, the thyroid, and long standing gastro-intestinal disturbances associated with anemia. Anoxia associated with anesthesia and blood loss as well as the toxic effect of certain anesthetic agents on the liver and direct surgical trauma are further contributory factors. In 62 patients in this series liver function determinations were routinely carried out by means of the hippuric acid excretion test (Table III). This was frequently checked by other function tests. The determinations were not performed on every patient, being reserved for those whose condition would seem to indicate further preparation for operation. In 48 patients (77.4 per cent) a definite decrease in liver function was detected, ranging from moderate impairment (an excretion of 0.6 to 0.8 Gm.) to severe impairment of the liver (below 0.5 Gm.). The frequent incidence of liver impairment in seriously ill patients has been pointed out by Boyce.[8] These figures would seem to corroborate his views and indicate in a striking manner the urgent need for careful supervision of these patients.

TABLE III

LIVER FUNCTION STUDIES AS DETERMINED BY THE HIPPURIC ACID TEST AND THE RELATIONSHIP TO POSTOPERATIVE PLASMA PROTEIN VALUES

		Diminished Hippuric Acid Excretion		Normal Hippuric Acid Excretion	
			No. of Cases		No. of Cases
Diagnosis	Operation	No. of Cases	with Fall in Proteins	No. of Cases	with Fall in Proteins
Chronic cholecystitis (2)*	Cholecystectomy	13	13	3	1
Acute cholecystitis (2)	Cholecystectomy	3	3	—	—
Obstructive jaundice (3)	Choledochostomy. Cholecystogastrostomy	4	4	—	—
Peptic ulcer (3)	Gastro-enterostomy	2	2	1	1
Carcinoma of stomach (3)	Gastrectomy or gastro-enterostomy	7	7	—	—
Perforated peptic ulcer (4)	Closure	—	—	1	1
Carcinoma of colon (3)	Resection	3	3	1	1
Chronic intestinal obstruction (3)	Entero-enterostomy	—	—	1	1
Acute pancreatitis (4)	Celiotomy or chole-cystostomy	3	3	—	—
Graves' disease (7)	Thyroidectomy	12	12	3	0
Nontoxic thyroid disease (9)	Thyroidectomy	—	—	2	0
Tubo-ovarian abscess (8)	Salpingo-oophorectomy	1	1	1	1
Subphrenic abscess (4)	Drainage	—	—	1	1
Totals		48	48	14	7

*Note: Figures in parentheses indicate to which group of Table I the cases belong.

The postoperative course of these cases with deficient liver function as contrasted with the group as a whole is of interest. Despite the fact that the patients in this group received better preoperative treatment by diet, transfusions and vitamins, every one showed a definite and usually prolonged drop in the plasma protein as contrasted with a percentage of 68.9 in the entire group and a percentage of 50.0 for those patients whose liver function was normal. Comparison of these percentages (100 per

cent in the group with poor liver function and 50 per cent in the group with normal liver function) yields a relative deviate of 5.2 which is well beyond the limit of significance. In other words, patients with diminished liver function can be expected to show a postoperative fall in plasma protein much more frequently than those with normal function. This trend is extremely suggestive and the conclusion almost inescapable. Unquestionably, two factors have operated in these cases: (1) A depletion of protein stores because of prolonged poor liver function; and (2) an inability of the liver to synthesize rapidly enough plasma protein to replenish that lost as a result of the operative procedures (blood loss, shock, anesthesia, *etc.*). In addition one might postulate the existence of a vicious cycle, inasmuch as continued low plasma protein concentrations and depleted protein reserves may have a harmful effect on liver structure and function. It was our impression, also, that the response in protein concentration as a result of blood or plasma transfusion in these cases was not as sustained, although usually as prompt, as in other cases whose liver function showed no evidence of deterioration.

It is of great significance to the surgeon therefore, that control of plasma protein formation and protein storage is a function of the liver and that in many patients and especially in certain groups of patients, the function of the liver is impaired. In these cases, the incidence of hypoproteinemia and of decline in the protein levels to low normal values will be extremely high and the postoperative course will be correspondingly stormy. The indications for therapy are derived from these facts.

PROPHYLAXIS AND TREATMENT

It is evident from the preceding data that certain types of surgical patients will probably lose considerable amounts of plasma proteins as a result of operative procedures, while in other groups the loss will be insignificant and rapidly restored. With the latter, we are not particularly concerned, but in the former group certain problems of therapy are of great consequence. From a therapeutic standpoint this group can also be divided into two subgroups:

Subgroup I.—In this classification fall those patients who are about to undergo certain major surgical procedures which we know are frequently or usually associated with a definite decline in the plasma protein levels. The liver function is normal, but the preoperative level of the plasma protein may be either normal or slightly lowered. It is very important in these cases to attempt to assess the presence and amount if any, of deterioration in the reserve stores of protein. Some patients may have normal values which are being maintained at the expense of exhaustion of the protein stores. While this may be difficult to evaluate by laboratory methods the clinical history is of great importance. The length of the illness, the previous dietary regimen, the probability of absorption of nutritive elements from the ingested foods and the presence of subclinical or clinical avitaminosis are guides to a proper evaluation. Of course, if the protein levels are low, one must assume that

the reserve has been more or less exhausted. If one so decides operation must be deferred except in the gravest emergency until the depleted proteins are replenished. This may be done by several methods. The best and most practical route of administration is by mouth. This is the natural route for the absorption of the products of protein metabolism and is usually the most efficacious. A high protein diet for one to two weeks usually gives excellent results. If for any reason this cannot be administered, concentrated amino-acid preparations may be used. We have used these on many patients in this group with satisfactory results and they have the further advantage of being easily administered through a duodenal tube if necessary. In order to obtain the maximum benefit from the protein diet or from the amino-acids, it is important to remember that all protein foods do not effect equal increments in plasma protein production. Certain key amino-acids are essential for this synthesis, and among these are cystine, tryptophan, tyrosine, leucine and glutamic acid. A definite quantitative difference in plasma protein synthesis can be obtained by feeding various amino-acids.[18] Milk, wheat, and eggs have a high cystine content and are, therefore, valuable in the diet. If amino-acids are fed as such, cystine and tryptophan should be present in large amounts. Preparations derived from casein, with tryptophan added, usually meet these requirements. If, for any reason oral feeding is interdicted, the intravenous route must be employed. For this purpose nothing gives results comparable to plasma transfusions. These should be given repeatedly and in large amounts and should be given to meet the requirements of the patient and not the convenience of the individual blood donor. Fortunately, with the increasing prevalence of blood banks the former usual arbitrary amount of 500 cc. per transfusion is rapidly becoming obsolete and transfusions of 1000 to 1500 cc. of blood or plasma are frequently administered with excellent results and no untoward reactions. In our experience the use of intravenous amino-acids has not been very successful, but we have not used this method extensively. Once the protein reserve and blood levels have been restored, operation may be safely undertaken.

In those patients whose protein stores are not depleted our concern is to prevent excessive declines in the plasma protein concentration. This drop in plasma proteins associated with operation will probably be transient and easily overcome by suitable administration of whole blood or plasma. The best guide to the quantity of blood and plasma required are serial studies of the hematocrit values and plasma protein concentration. It has been our experience that a transfusion of 500 cc. to 1000 cc. of plasma immediately preceding or during operation will carry these cases through any but the most shocking procedures.

Subgroup II.—This includes those patients in whom an impairment of liver function can be demonstrated and who are about to undergo major surgical procedures. In this group, also, the protein levels may be normal or low but in all probability, there has been some depletion of the protein stores. We are faced, in these patients, not only with the problem of restor-

ing the reserve stores of protein but with improving liver function, and in addition protecting the liver from further impairment of function as a result of anesthesia, operative shock and anoxemia.

Glucose has long been considered the substance *par excellence* for improving liver function. It is not to be denied that glucose in sufficient quantities does exert a markedly beneficial effect. It is the principal source of energy for the body mechanism and has the specific physiologic effect of sparing proteins. Recent evidence,[19, 20, 21] however, has indicated that proteins are probably much more efficacious in restoring and maintaining good liver function. This experimental evidence points out that livers with a high lipid content are much more susceptible to toxins than those with a low lipid content. Wells[34] has suggested that a large amount of liver fat results in a retention of lipid soluble hepatotoxic agents. It has been known for many years that fatty changes in the liver are associated with poor function. Proteins are effective in reducing liver fat.

The therapeutic effect of proteins is probably two-fold in patients with liver damage. In the first place, regeneration of body tissues requires ample protein supplies, and, secondly, protein undoubtedly has a specific effect in protecting the liver from injury. This action is probably a result of the lipotropic activities of certain amino-acids. Moise and Smith,[22] Miller, Ross and Whipple,[19] Goldschmidt, Vars and Ravdin,[20] Messinger and Hawkins,[23] and Perlman, Stillman and Chaikoff[24] have demonstrated the protective effect of proteins on the liver. Certain substances are known to be lipotropic; that is, they mobilize liver lipid and make it available for easy disposition. Lipocaic, choline and lecithin have marked lipotropic activity. Of the amino-acids, methionine and cysteine are the principal lipotropic agents. The former is more efficacious, inasmuch as cysteine has only a temporary lipotropic effect. In fact, after prolonged administration, it may exert an opposite effect. Other amino-acids including glycine, alanine, tyrosine, taurine, glutamic acid, and proline have no lipotropic activity. Choline is thought to be necessary for the action of any lipotropic substance. This may account for the deterioration of liver function in patients with biliary fistulae and persistent loss of bile. It is significant that cysteine is a key amino-acid for plasma protein regeneration also, while methionine is of no value in this process, but is more important for its lipotropic activity.

The foregoing evidence has a definite clinical application. It can be said that the most favorable diet for patients in this group should contain ample carbohydrate for energy purposes and to spare protein, ample protein containing sufficient amounts of lipotropic substances, and as little fat as is compatible with a palatable diet. Meat, in general, is not satisfactory, inasmuch, as even lean meat contains considerable fat. Channon and Wilkinson[25] state that a diet in which more than 14 per cent of the total calories are obtained from proteins will exert a marked lipotropic action. Casein, or foods high in casein are undoubtedly the best. Tucker and Eckstein[26] demonstrated the greatest decrease in liver fat with a 20 per cent casein diet.

A hospital diet containing 75 per cent of carbohydrates, 20 per cent of proteins (no meat) and 5 per cent fat will fulfill these requirements.

If food cannot be taken by mouth the same considerations should govern the parenteral therapy. However, it is difficult to supply sufficient glucose intravenously to meet the energy requirements of the body. A total of 1200 calories daily is the net result of 3000 cc. of 10 per cent glucose solution. The disadvantages of parenteral glucose are two-fold: first, the inconvenience of daily intravenous therapy and the danger of thrombosed veins, and secondly, the inadequacy of the amounts administered and the probability that glucose by mouth is more efficacious in its action on the liver than intravenous glucose. It is preferable whenever possible to supplement the intravenous therapy with some carbohydrate by mouth. This may be given as concentrated glucose solution.

Protein is best given parenterally in the form of plasma. While amino-acids have been used with some success by others, we have been unable to show any beneficial effect on the liver or any sustained rise in the plasma proteins by this method. However, our experience has not been very large with intravenous amino-acids therapy. One point is worth noting in this connection. It has been stated previously that cysteine exerts an initial lipotropic effect but prolonged administration nullifies this early action. It is thought that the cysteine which is present in plasma does not show this late change however, and plasma may be given indefinitely for its lipotropic action. This may account for our failure to realize any appreciable benefit with amino-acid solutions while with plasma the results were most encouraging.

Other measures have been suggested to improve liver function. The administration of Vitamin B_1 may be of value. Connor[27] has shown that deficiency of this vitamin may cause fatty infiltration of the liver. Furthermore, Vitamin B-complex is necessary for certain intermediary stages of carbohydrate metabolism and oxidative reactions in the tissue cells. The importance of this adjuvant when large amounts of carbohydrates are being fed to the patient is obvious. Bile salts and liver extracts are also indicated in certain cases. The marked lipotropic activity of choline has been mentioned and liver extract is rich in choline. The bile salts of taurocholic and glycocholic acids may have a similar effect. It is certainly well known that excessive loss of these bile salts has a deleterious effect on liver function.[28, 29, 30] Bile salts administered orally also increase the arterial blood flow to the liver,[28] a real consideration in combating anoxia. Schmidt, Walsh and Chesky[31] have found that insulin causes improvement in poor liver function associated with toxic thyroid disease. They feel that the damaged liver due to thyroid disease reacts differently to insulin than the normal liver in which it is well recognized that insulin is of little value in promoting glycogenesis.[32, 33] Further observations are undoubtedly necessary to determine the effect of insulin on livers damaged as a result of other conditions. We have not used it on the patients in this survey.

It was our experience with patients in this group that marked improvement occurred within two weeks as a result of the therapy instituted, except in some patients whose hippuric acid excretion was below 0.3 Gm. While it was not always possible to restore hepatic function to normal, we usually obtained satisfactory improvement, as manifested by a definite increase in the hippuric acid excretion. The optimum time for operation was occasionally difficult to determine and depended on many individual variations. The concomitant improvement in the protein reserve and the return to normal of the plasma protein values as a result of treatment directed at improving liver function are factors which aid in making a decision. In this group of patients we also observed a postoperative decrease in liver function below the maximum preoperative level, in spite of our prophylactic measures. The diminution was usually transient, but served as a danger signal and indicated the importance of fortifying the liver before operation.

In this second group, as contrasted to the first, in whom hepatic function was normal, extreme vigilance was required for many days after operations to forestall delayed protein declines. In the first group, once the immediate postoperative fall in proteins was compensated for, the level remained stationary unless complications developed. In the second group, however, even though improvement in liver function had been obtained, the return to normal of the plasma proteins was delayed, and was subject to many fluctuations. Continuation of the preoperative regimen was found to be essential to rapid and uncomplicated recovery.

The following case reports were selected in an attempt to illustrate more graphically the problems involved in the prophylaxis and treatment of the various phases of protein depletion and concomitant liver dysfunction.

CASE REPORTS

Case 1.—A. A., Hosp. No. 90176. Acute suppurative appendicitis. Appendicectomy. A drop in plasma protein concentration of 1.1 Gm.% occurred within 48 hours, despite a simple operative procedure. Return to the preoperative level did not take place until the eighth day. No special therapy was employed. We believe that there is a continuing loss of plasma into the peritoneal cavity for several days after operations for acute appendicitis, and this frequently accounts for prolonged diminution in the protein levels.

Case 2.—F. A., Hosp. No. 88080. Appendiceal abscess. Appendicectomy and drainage (wound packed open with iodoform gauze). Preoperative levels: Plasma proteins 7.0 Gm.%; hematocrit 42%. The protein level was maintained fairly well for two weeks. During this period drainage from the wound was profuse, and the patient had a moderate febrile reaction. The food intake was limited. The protein concentration began to fall quickly at the 14th day, probably due to exhaustion of protein reserves. This decline persisted until the 36th day (plasma proteins 6.2 Gm.%; hematocrit 42%), at which time intensive amino-acid therapy by mouth was instituted. Recovery was rapid after this point. Incidentally, during the first five weeks, wound healing was very slow but immediately after beginning amino-acid therapy a marked increase in the rate of granulation of the wound was observed.

Case 3.—K. K., Hosp. No. 89481. Chronic cholecystitis and cholelithiasis. Cholecystectomy. Preoperative studies indicated good liver function, normal plasma protein concentration, and apparently adequate protein reserves (plasma proteins 7.2 Gm.%;

hematocrit 44%; hippuric acid excretion 1.24 Gm.). Operation was carried out without any special preparation and the postoperative course was uneventful. There was an immediate and definite drop in both protein levels and liver function (plasma proteins 6.3 Gm.%; hematocrit 42%; hippuric acid excretion 0.49 Gm.), probably as a result of blood loss, operative trauma and anesthesia, but the declines were transient and a return to normal figures was noted on the 9th postoperative day. For purposes of therapy this patient should be classified in Subgroup I.

Case 4.—M. R., Hosp. No. 90200. Chronic cholecystitis and cholelithiasis. Cholecystectomy. Liver function studies indicated very poor function, and the low hematocrit and plasma protein figures indicated depletion of protein stores and a moderate secondary anemia (plasma proteins 6.1 Gm.%; hippuric acid 0.10 Gm.; hematocrit 33%). Dietary therapy was instituted for two weeks preceding operation, and while improvement in the protein concentration was satisfactory, liver function remained poor (0.51 Gm.). At operation, a walled-off pericholecystic abscess was found. The postoperative course was stormy, with elevated temperature and increased pulse rate for almost one week. With continuation of the dietary regimen, liver function gradually improved and the protein figures reached the preoperative level on the 14th postoperative day. This case was definitely in Subgroup II. More intensive protein therapy should have been administered in the form of plasma or whole blood transfusions.

Case 5.—A. C., Hosp. No. 89875. Graves' disease. Thyroidectomy. Liver function was markedly depressed but the proteins were normal (plasma proteins 6.6 Gm.%; hematocrit 46%; hippuric acid excretion 0.39 Gm.). Fairly intensive preoperative therapy was administered, but emphasis was placed on the thyroid rather than on the liver. A moderate postoperative crisis developed, associated with substantial protein depletion. Glucose and proteins were fed in large amounts with a satisfactory but very slow response.

Case 6.—C. P., Hosp. No. 86521. Graves' disease. Second-stage hemithyroidectomy. In the interval between operations the liver function and protein reserves were thought to be restored to normal (plasma proteins 6.7 Gm.%; hematocrit 33%; hippuric acid excretion 1.2 Gm.). However, the operative time was prolonged to two hours, and there was moderate bleeding. The effect on the protein was marked and sustained, a drop to 5.4 Gm.% occurring within three days after operation. On the 8th day the values had returned to normal. Apparently, this patient had not been sufficiently fortified for operation.

Case 7.—S. M., Hosp. No. 87843. Toxic adenoma of the thyroid. Hemithyroidectomy. Because of the satisfactory results of liver function tests and the adequate plasma protein level (plasma proteins 7.2 Gm.%; hematocrit 46%; hippuric acid excretion 1.5 Gm.%) no special treatment was thought necessary beyond that directed at the toxic thyroid disease. As in the preceding patient, the postoperative decline in protein levels and hippuric acid excretion was significant and fairly prolonged. The plasma proteins declined to 6.0 Gm.% on the third day, and remained low for over one week.

Case 8.—B. R., Hosp. No. 87569. Nontoxic adenoma of the thyroid. Hemithyroidectomy. The preoperative nutritional status was good (plasma proteins 7.9 Gm.%; hematocrit 45%; hippuric acid excretion 1.14 Gm.) and operation was performed the day following admission to the hospital. An immediate decline of 1.3 Gm.% in the protein values was observed, probably the result of excessive blood loss during a two hour operation. The return to normal was rapid, however, indicating that protein reserves were ample. This patient would be classified in Subgroup I, as contrasted to the preceding cases of toxic thyroid disease.

Comment.—A study of the four preceding cases of thyroid disease indicates the necessity for appreciating the significance of the liver and the protein reserves. Patients with toxic thyroid disease may show normal liver function preoperatively but they are potential "liver weaklings" and the effects of operation, blood loss, anesthesia and the resultant often prolonged

anoxia may be disastrous. Prolonged preparation not only for the hyperthyroidism, but for the liver is essential. We believe that more frequent blood or plasma transfusions would decrease the incidence of postoperative thyroid crisis.

Whereas the decline in proteins in the nontoxic cases is of very short duration, in the patients with hyperthyroidism the return to normal is delayed and is associated with postoperative impairment in liver function. The usual high carbohydrate diet which is fed to these cases preoperatively is insufficient and should be replaced by a diet rich in protein and very low in fat.

Case 9.—C. G., Hosp. No. 89429. Chronic, perforating duodenal ulcer. Subtotal gastrectomy. Preoperative studies of liver function and plasma proteins revealed normal levels (plasma proteins 7.0 Gm.%; hematocrit 42%; hippuric acid excretion 0.85 Gm.). At operation, a transfusion of 500 cc. of whole blood was given. Despite this, a marked decline in proteins to 5.3 Gm.% occurred immediately, and persisted for 16 days. On the tenth day, amino-acids were given orally, and continued daily. The effect was not manifested for several days however, but eventually a definite gain was observed. The amino-acids therapy was started at the time when the protein concentration was definitely below the edema level, and peripheral edema was present. While the patient had normal liver function and should be classified in Subgroup I, we feel that in common with most patients with chronic peptic ulcers she had a marked depletion of her protein reserves.

Case 10.—L. C., Hosp. No. 90438. Posterior wall gastric ulcer, with perforation into the pancreas. High subtotal gastrectomy. A week of preparation with a high protein diet before operation was thought to be adequate, although hepatic function was still subnormal (plasma proteins 6.5 Gm.%; hematocrit 37%; hippuric acid excretion 0.64 Gm.). During the operation 500 cc. of plasma were administered. An immediate rise in proteins took place followed by a moderate decline of 1 Gm.%. The hippuric acid excretion also diminished. A slow upward swing occurred during the next 10 days, but upon discharge from the hospital, on the 13th postoperative day, the preoperative levels had not been reached. In this patient, again, a fairly normal plasma protein concentration was maintained at the expense of exhaustion of the protein reserves and the customary restoration of proteins lost as a result of operation was delayed and inadequate.

Case 11.—L. B., Hosp. No. 88177. Carcinoma of the stomach at the esophagogastric junction. Gastrectomy. The preoperative protein level was normal, and the general nutritional status appeared good, inasmuch as the patient had lost only three or four pounds. No liver function tests were performed (plasma proteins 7.4 Gm.%; hematocrit 49%). Owing to marked technical difficulties, operation was prolonged to four hours, and 500 cc. of whole blood were given on the operating table. A drop of 1.5 Gm.% in plasma proteins occurred in the first 48 hours. During this time, a massive atelectasis of the right lung developed, which was successfully treated by bronchial aspiration. On the second day 1000 cc. of whole blood were given, and an increase in protein concentration to 6.3 Gm.% followed. Feeding of amino-acids through a stomach tube, which was drawn through the anastomosis at the time of operation was started on the 5th postoperative day and another transfusion was administered two days later. The result of this therapy was eminently satisfactory, and a sustained high protein level was secured. A persistent elevation of the hematocrit reading despite absence of any clinical evidence of dehydration was an interesting finding.

Case 12.—F. R., Hosp. No. 89683. Benign pyloric obstruction. Gastro-enterostomy. This patient was considered a good operative risk and classified in Subgroup I (plasma proteins 7.0 Gm.%; hematocrit 44%; hippuric acid excretion 0.80 Gm.). Liver function was within normal limits. The operative procedure was easily and quickly performed

and 500 cc. of blood administered. The protein levels remained fairly stationary for the first week, but during this time the patient took very little food and was unable to tolerate amino-acids by mouth. Thereafter the proteins dropped considerably and reached 5.9 Gm.% on the 16th day. At this point, adequate feedings were satisfactorily instituted and a prompt response obtained. This case illustrates, again, the lack of protein reserves in patients with gastro-intestinal disturbances.

Case 13.—J. G., Hosp. No. 88423. Chronic obstructing duodenal ulcer. Gastro-enterostomy. This case is included to demonstrate the value of proper therapy. Intensive preoperative therapy with amino-acids by mouth and a high protein diet was instituted to replenish the protein reserve. The preoperative plasma protein level was 6.4 Gm.%, and the hematocrit was 40%. At operation, a transfusion of 600 cc. of blood was administered. A slight drop in proteins was observed, but this figure is misleading, inasmuch as marked hemoconcentration was present. Nevertheless, with amino-acid therapy through an indwelling tube, started on the 3rd postoperative day, a prompt rise in the proteins to a level above the preoperative figure was secured and maintained. Feedings by mouth were started on the 6th day, and the tube withdrawn.

Comment.—It became apparent to us that practically all patients with a long-standing gastro-intestinal disorder suffered depletion of their protein reserves in spite of normal plasma protein levels. Occasionally liver function was subnormal, probably as a result of malnutrition due to a deficient diet. In these patients a determined effort must be made to build up the protein reserve before operation and sustain this reserve after operation by transfusion and an easily assimilable protein diet. Neglect of these precautions was responsible for nutritional edema in two of our cases and contributed to a stormy and prolonged postoperative course in others. Feeding of amino-acids through an indwelling tube, which is drawn through the anastomotic stoma at the time of operation, can be started on the third or fourth postoperative day and serves admirably to maintain the protein level. When blood or plasma is not readily available this treatment is of tremendous value.

Case 14.—G. P. Hosp. No. 89360. Carcinoma of the breast. Radical mastectomy. The effect of excessive blood loss at operation is well illustrated by this case. The preoperative status was perfectly normal except for a carcinoma of the breast (plasma proteins 7.35 Gm.%; hematocrit 37%). The operation lasted one hour and fifty minutes, and blood loss was thought to be marked. A decline of 1.3 Gm.% in the plasma proteins occurred, but was fairly rapidly restored. The capacity of the average patient to replenish proteins lost as a result of hemorrhage is excellent.

Case 15.—G. K., Hosp. No. 88018. Ruptured peptic ulcer. Closure of perforation. Operation was performed immediately after admission, at which time the plasma proteins were 6.1 Gm.%, and the hematocrit 42%. This low level of plasma proteins was undoubtedly due to the moderate degree of shock following perforation of the ulcer. A further decline of 0.65 Gm.% was observed postoperatively, but within five days the proteins attained a level of 6.9 Gm.%, which was probably the normal figure. The convalescence of this patient was uneventful.

Case 16.—J. E., Hosp. No. 88206. Charcot hip. Arthrodesis. The preoperative figures were normal (plasma proteins 7.2 Gm.%; hematocrit 46%). The operation was extremely shocking and blood loss was great. A transfusion of 500 cc. at the time of operation was not sufficient to prevent the combined effects of shock and hemorrhage from lowering the protein level 1.6 Gm.%. Two subsequent transfusions were administered, but recovery was slow, and after 18 days the proteins had only reached 6.8 Gm.%. Obviously, further therapy with transfusions should have been administered.

Comment.—The relative effects of shock, hemorrhage, and both shock and hemorrhage together, are illustrated by the three preceding cases. Simple hemorrhage produces an effect which can be remedied fairly quickly. Shock, unaccompanied by hemorrhage, and insufficient in itself to cause irreversible changes, can also be rapidly balanced. When, however, both occur simultaneously the effect on the protein levels is much more marked and prolonged and must be strenuously treated without delay. Therefore, before starting operations which are known to be productive of shock and hemorrhage, transfusions should be commenced and continued until the operation is completed.

Case 17.—R. K., Hosp. No. 88563. Bleeding uterine fibroids. Hysterectomy. This patient had a severe secondary anemia as a result of repeated hemorrhages. The hematocrit was low, but the proteins were normal (plasma proteins 7.2 Gm.%; hematocrit 28%). A transfusion was given during the operation, but the protein concentration dropped 1.1 Gm.%, nevertheless. Another transfusion was given on the 3rd postoperative day, and thereafter the hematocrit and protein values returned to normal. This case illustrates the effect of severe anemia on the postoperative decline of plasma proteins. An operation which ordinarily causes but slight depletion of the proteins, was responsible for a significant loss in this patient, despite a transfusion of 500 cc. of whole blood.

Case 18.—R. S., Hosp. No. 87996. Uterine fibroids. Postoperative intestinal obstruction secondary to carcinoma of the sigmoid. Hysterectomy. Cecostomy. Preoperative: Plasma proteins 6.8 Gm.%; hematocrit 42%. A simple hysterectomy was performed upon this patient, and a very slight immediate drop in proteins occurred. On the third postoperative day signs of intestinal obstruction developed, and these persisted. A marked decline in plasma proteins to 5.7 Gm.% was observed during this period. On the sixth day a cecostomy was performed and a transfusion administered. A slight response to the transfusion occurred but the proteins subsequently dropped to still lower levels (5.5 Gm.%) and for a period of 10 days the cecostomy functioned poorly. When the abdominal distension was finally overcome with a Miller-Abbott tube the plasma protein levels gradually returned to normal. The importance of repeated determinations of plasma protein levels in patients with actual or impending intestinal obstruction is well illustrated by this patient.

SUMMARY AND CONCLUSIONS

A significant decline in the plasma protein level was demonstrated in a considerable number of patients following surgical procedures. In a nonselective group of 215 patients, this decline was observed in 148, or 68.9 per cent. Our studies further indicated that a postoperative decline in plasma proteins was more common after certain types of operations. In this group were included operations upon the stomach and intestines, the biliary tract, the spine and large joints, and upon toxic thyroid disorders.

A combination of many factors influenced the extent and duration of the diminished protein concentration. Among the direct and immediate causes were blood loss, shock and anesthesia, while among the indirect causes were the nutritional status of the patient and extent of the protein reserves and the adequacy of liver function. The depreciation of plasma proteins as a result of blood loss and shock was usually of short duration and readily amenable to therapy, if it did not quickly and spontaneously return to

normal. When the protein reserves were exhausted or liver function was disturbed, the duration of protein depletion was prolonged and frequently the response to treatment was irregular.

The presence of subnormal hepatic function as demonstrated by the hippuric acid excretion test was a certain indicator that a postoperative protein decline would occur. Impairment of liver function was observed in 48 patients in this series, and a substantial diminution in the plasma protein concentration occurred in each case. Inasmuch as liver physiology is known to be disturbed frequently in certain surgical conditions of an extrahepatic nature, it is essential that liver function tests be performed routinely in these cases. Included in this category are patients with biliary disease, hyperthyroidism, severe gastro-intestinal disease associated with malnutrition, severe anemia, and carcinoma. The results of these tests should act as a guide for therapy.

The treatment of plasma protein depletion depends on the extent and duration, the amount of available protein reserves, and the adequacy of liver function. Since certain operations are known to be almost constantly associated with marked protein loss, the estimated loss should be replaced during the operation by blood or plasma transfusions. In patients with normal liver function and adequate protein reserves, this substitution will be the only treatment necessary and operation need not be delayed. If the protein reserves are thought to be exhausted postponement of the operation is indicated until the reserves can be restored. Dietary therapy is particularly valuable in these patients and should consist of a high protein diet which contains ample amounts of food with high contents of certain key amino-acids. If this diet cannot be administered amino-acids may be fed with satisfactory results.

In the group of patients with liver damage (Subgroup II) therapy should be directed to a restoration of normal hepatic function. It has been shown that the lipid content of the liver is an index of the ability of this organ to function adequately. A high lipid content is deleterious. Furthermore, there is evidence that proteins, and more particularly certain amino-acids such as methionine and cystine, have a great lipotropic effect; that is, they mobilize liver lipid and make it easily available for disposition. Therefore, in order to restore liver function to normal, ample amounts of selected proteins must be given along with sufficient carbohydrate to supply energy requirements. Plasma is a readily available and potent source of the necessary proteins and often proves efficacious when dietary therapy fails.

A study of the cases included in this series reveals that a proper therapeutic regimen is often neglected, and patients are operated upon before they are adequately prepared. We feel, that with proper preparation in the preoperative period, the extensive decline in the plasma proteins which were exhibited by these cases could be prevented frequently. Routine determinations of liver function should be made on all patients about to undergo major surgical procedures, and when possible, operation should be delayed until

restoration of adequate liver function is accomplished. Careful supervision of the diet and the more frequent use of plasma transfusions for their nutritional effect would enable most patients to avoid the threatened hypoproteinemia associated with the operations under discussion. Recently, by applying the therapy outlined above, we have been able to prevent, or greatly minimize, these declines in plasma protein concentration.

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CARCINOMA OF THE GUM

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SQUAMOUS CELL CARCINOMA arising in the buccal mucosa which covers the alveolar margin differs completely in its behavior from similar neoplasms which arise from other areas in the mouth and pharynx. The primary lesion is, from its origin, in close proximity to bone, and invasion of the bone occurs very early. It invades the bone widely while the visible area of ulceration remains small and sometimes innocent in appearance. The destruction of bone by the neoplasm and by infection which follows it give rise to pain. Unlike malignant disease in other areas in the body, pain may be a fairly early evidence of the disease, and the surgeon is consulted in many cases where the disease involves a small part of the soft tissues and is otherwise contained within the rigid and limiting structure of the jaw. This particularly applies to the cancer which arises on the lower alveolus and invades the mandible. This communication is concerned with the establishment of this lesion as an entity and with the treatment of cancer of the lower alveolus based upon knowledge of its usual mode of spread.

The term cancer of the gum has recently been applied to this lesion by Martin.[1] "Cancer of the jaw" or "carcinoma of the mandible" have been most frequently applied in the past, and these terms have been used to include carcinoma arising anywhere in the buccal mucosa and secondarily invading the mandible. New,[2, 3] in recent articles on the treatment of oral carcinoma, speaks of epithelioma of the lower jaw which "may originate in a previous papillary leukoplakia or the first symptoms may be a loosening of a tooth, starting in the body of the jaw." Probably squamous cell carcinoma and adamantinoma are grouped together, treatment of the lesions being disposed of by the simple statement that thorough destruction of all precancerous and malignant lesions with surgical diathermy gives the best chance of permanently getting rid of the trouble. As opposed to numerous reports on the treatment of oral cancer in which carcinoma of the lower alveolus is considered lightly, or not at all, other authors have set it aside as a problem more difficult to treat than other lesions of the mouth. Gardham[4] calls attention to the extreme degree of malignancy usually present, and states that with five personal cases the longest survival period is two years. Resection of the mandible and primary bone graft was performed in this case. Blair, Brown and Byars[5] called attention several years ago to the frequent need for complete destruction of the mandible following the use of radium in lethal doses, and advised against radiation of the bone, even where its use is effective in the soft tissues Shaw,[6] and Ehrlich,[7]

have discussed at length necrosis of bone as related to the use of radiation therapy, and both report the rare incidence of cures but do not suggest that other forms of therapy might be practiced in an effort to improve the rate of cure and to add to the comfort of patients. Albright,[8] in 1935, published a complete review of the recent literature pertaining to the accepted methods of treatment of oral carcinoma, and stated that radiation here offers little. Primary destruction or excision without preliminary radiation is not sug-

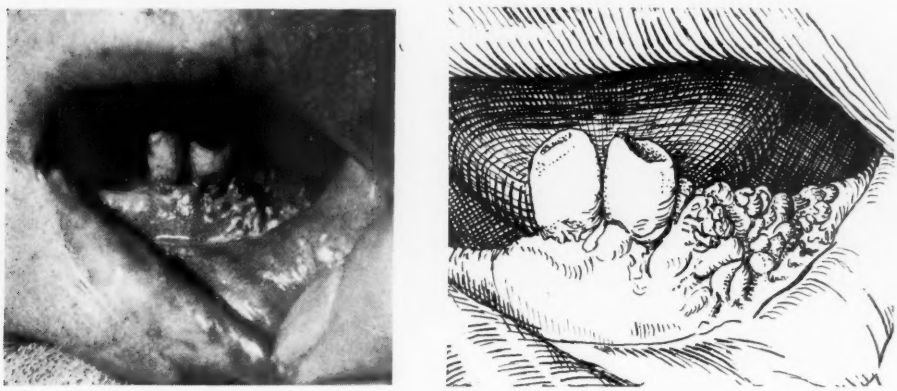

FIG. 1-A and B.—Case No. 3: Before operation.

gested, however. Martin[1] emphasizes the importance of alveolar carcinoma as a distinct anatomic form of intra-oral cancer, and states that it has received less attention than its relative frequency merits. As regards treatment, Martin states that "radiation (x-ray) therapy is the most useful and suitable method of treatment, since in the average case the growth in the gum is situated posteriorly, is over three centimeters in diameter, and involves at least one neighboring relatively inoperable structure." He advises the use of surgical excision in only the very earliest superficial lesions and employs roentgenotherapy by means of a carefully centered metal cylinder, through the open mouth. There were 57 malignant growths of the lower gum (about 95 per cent of which were squamous cell carcinoma), 15, or 26 per cent, of which are living without evidence of recurrence five years after treatment. About one-fourth of the patients treated by roentgenotherapy subsequently developed radio-osteomyelitis, with some loss of bone. These results are superior to others which have been reported, and are important also because only those lesions which originate in the buccal mucosa which overlies the alveolus are included.

THE TREATMENT OF CARCINOMA OF THE LOWER GUM AT THE VANDERBILT UNIVERSITY HOSPITAL

Prior to 1933 all cases of carcinoma of the gum seen in this clinic were treated either by roentgenotherapy or by radium, and no cures were obtained. Since 1933 cautery excision of the mandible, performed in much the same manner as was described by Bloodgood,[9] and more recently by Blair, Moore and Byars,[10] has been advised whenever it was thought that

the lesion might possibly be completely excised. The operative procedure has in most cases been supplemented by roentgenotherapy over the neck, but in no case which was thought to be operable was radiation of the primary lesion advised. At the time of operation the prime consideration has been eradication of the neoplasm. We believe that the fear of unsightly facial defects frequently influences the surgeon to perform limited intra-oral operations, as well as in the application of roentgenotherapy in empiric doses which are inadequate to destroy carcinoma which is growing in the mandible. Such procedures, carried out in patients with early lesions, are often worse than worthless, since longevity is not usually increased and the patient is subjected to the discomfort attending these forms of treatment.

FIG. 2.—Case No. 3: Roentgenogram before operation.

Since 1933 there have been 111 patients observed with squamous cell carcinoma of the buccal mucosa and the lower lip in the Vanderbilt University Hospital. Fifty-nine of these began in the mucous membrane of the mouth itself (excluding the lip and the pharynx). Thirty, or 51 per cent of these growths apparently originated in the gum. Two arose in the gum of the upper alevolus, and 28, or 47.5 per cent, of these lesions began as an ulcer on the lower alveolar margin.

Four years have now elapsed since 23 patients with squamous cell carcinoma of the lower gum were first observed. Twelve of these patients were operated upon. A summary of the results in these cases is shown in Table I. The outcome in the remaining 11 cases is presented in summary in Table II. The technic of operation was the same in all but two patients in Table I. In these cases (Nos. 2 and 5), destruction of the full thickness of mandible was purposely not accomplished and the continuity of the inferior portion of the mandibular arch was preserved following sequestration.

TABLE I

OPERATION—CAUTERY RESECTION OF MANDIBLE

Case No.	Age	Color	Sex	Duration of Early Symptoms	Postoperative Roentgenotherapy to Neck	Time of Sequestration of Mandible	Result: Alive and Well. Time Since Operation	Result: Dead. Time After Operation	Result: Dead. Time After Onset of Symptoms	Result: Dead. Cause of Death
1.	38	W.	F.	Ulceration 6 mos. Pain 1 month.....	2700 R.	10 weeks		7 mos.	13 mos.	Recurrence
2.	56	W.	F.	Ulceration 2 mos. Pain 2 weeks.....	6600 R.	20 weeks	4 years			
3.	51	W.	M.	Ulceration and tumefaction following extraction 3 mos.†.....	3280 R.	14 weeks	5½ years			
4.	57	W.	F.	Ulceration found by dentist 3 mos.†.....	6000 R.	8 weeks		11 mos.	14 mos.	Recurrence
5.	57	C.	M.	Ulceration 2 mos.....	1360 R.	8 weeks		12 hrs.		Cerebral accident (?)
6.	54	W.	M.	Ulceration 4 mos. Pain 1 month.....	None		6½ years			
7.	40	W.	F.	Soreness of jaw 12 mos. Bleeding 2 mos.....	3600 R.	20 weeks	5 years			
8.	73	W.	M.	Pain 4 mos. Ulceration about 24 mos.....	800 R.	16 weeks		10 mos.	14 mos.	Recurrence
9.*	77	W.	M.	Ulceration 6 mos. Soreness 3 mos.....	4500 R.	18 weeks		24 mos.	30 mos.	Recurrence
10.	57	C.	M.	Ulceration 5 yrs.† Pain 2 mos.....	6600 R.	12 weeks	4 years			
11.	74	W.	M.	Ulceration 5 mos. Pain 4 mos.....	6200 R.	16 weeks		3 years		Senility. No Recurrence
12.	36	W.	M.	Ulceration 2 yrs.† Pain 4 mos.....	None	12 weeks	4 years			

*9000 R. units, low voltage roentgenotherapy, using intra-oral cone, completed two months before operation (given elsewhere by competent Radiologic Clinic).
†Areas of ulceration failed to heal following tooth extractions.

TABLE II

OPERATION NOT PERFORMED

Case No.	Age	Color	Sex	Duration of Early Symptoms	Reason Operation Not Performed	Treatment	Duration of Life After First Appearance of Symptoms
13.	49	W.	M.	Ulceration 8 mos. Pain about 7-8 mos.....	Far advanced	Superficial X-ray (elsewhere)	10 mos.
14.	65	W.	M.	Ulceration 8 mos. Pain 3-4 mos.	Far advanced	None	12 mos.
15.	61	W.	F.	Ulceration and pain 12 mos....	Far advanced	X-ray refused	13 mos.
16.	53	W.	F.	Pain and ulceration 3 mos.....	Far advanced	X-ray 3600 R.	5 mos.
17.*	60	W.	M.	Pain and persistent ulcer following tooth extraction 4 mos.....	Refused	None	17 mos.
18.†	53	W.	M.	Ulceration and pain 6 mos.....	Far advanced	Radon: 7680 mc. hrs. (elsewhere). X-ray 6900 R.	17 mos.
19.†	51	W.	M.	Ulceration and pain 11 mos....	Far advanced	X-ray 2700 R.	17 mos.
20.*	46	W.	F.	Ulceration 7 mos. Pain 3-4 mos.	Refused	X-ray 4000 R.	16 mos.
21.*	58	W.	F.	Pain and ulceration 5 mos.....	Refused	X-ray (elsewhere)	13 mos.
22.*	74	W.	M.	Ulceration 3 mos. Pain 2 mos.	Refused	X-ray 2200 R.	26 mos.
23.*	61	W.	M.	Pain 3 mos. Ulceration 2 mos.	Refused	X-ray (elsewhere)	7 mos.

*Considered to be operable when first examined by us. Patient refused operation.
†Local removal by cauterization and application of radium performed elsewhere before patient first seen at Vanderbilt Hospital.

TECHNIC OF OPERATION

An incision is made beginning at about the symphysis of the mandible and is extended outward and down to the level of the hyoid bone under the body of the mandible. The incision there curves upward to extend slightly above the angle of the mandible. The skin and subcutaneous tissue of the flap are elevated, the incision being extended through the labial mucous membrane into the mouth. A suprahyoid neck dissection is then carried out, the incision being carried entirely through the muscles and mucous membrane of the floor of the mouth and care being taken to carry the incision through healthy tissue well away from the edges of the growth. The lip and skin flap are retracted upward, and moist saline packs are applied to cover the soft tissue of the neck, face and the mouth. The soft tissues adherent to the body of the mandible are excised, usually with the electrocautery. Hot soldering irons are used to cauterize the mandible and are applied for a sufficient length of time to assure destruction of the whole thickness of the bone and all of its attached soft parts. The mandible is not divided. The external skin flap is then brought back down into place and a few interrupted sutures are placed in the ends of the wound, its central aspect being left open. Flat packs of gauze are placed in the defect, against both sides of the mandible and a firm external dressing is applied.

A tube is frequently passed into the stomach, through the nose, for feeding purposes.

Chloroform anesthesia has been used in all cases, administered through an endotracheal catheter.

PREOPERATIVE AND POSTOPERATIVE MANAGEMENT

All patients are given high carbohydrate, high protein diets for two days before operation, with added frequent feedings of sugar. An adequate intake of fluid before operation is assured.

As soon as the patient is fully reacted, he is allowed to assume a sitting or semisitting posture. Feeding is usually accomplished during the first few days by means of the inlying stomach tube. All patients are gotten out of bed as soon as possible following operation and are encouraged to increase their activity as rapidly as can be tolerated.

Drainage from the wounds becomes fairly profuse and of a foul nature during the second week after operation. Following this period, during which slough of necrotic soft tissue occurs, the wound rapidly becomes cleaner, the fistula smaller and drainage less marked. Care is taken in the instruction of patients regarding the frequent taking of liquid and soft foods, and on discharge from the hospital the patient is given a list containing various essential foods to be included in his diet. Dressings are changed as frequently as may be desirable at home.

Separation and discharge of the dead mandible occurs in from two to five months following operation (average time 14 weeks). In most instances the bone has been easily lifted out of the wound during a regular follow-up

FIG. 3-A

FIG. 3.—Case No. 3: A and B. Appearance of sequestrum three and one-half months after operation.

FIG. 3-B

visit to the Tumor Clinic. Following sequestration, the opposite mandible swings a little toward the midline, and the fistula becomes somewhat smaller and quite clean. The patient is readmitted to the hospital a few weeks later and closure of the oral fistula is accomplished.

The appearance of the patient following closure of the fistula has been satisfactory in most cases. If there is no recurrence of the lesion after a year, plastic procedures may be carried out for the restoration of the continuity of the mandibular arch and improvement in the cosmetic results. In most cases these procedures will be refused by the patient.

The functional result is equally satisfactory. Speech is not seriously interfered with and the mastication of soft foods can be accomplished.

FIG. 4.—Case No. 3: Roentgenogram three and one-half months after operation, just before removal of mandible.

DISCUSSION

The earliest symptom in most cases has been ulceration of the gum. This has been followed within a few weeks by soreness and then by pain in the jaw. All but four of the 23 patients presented themselves for examination after the onset of pain and 17 patients (74 per cent) were advised to have operation.

The average duration of symptoms in the group of patients operated upon was six and one-half months. In those who were inoperable the average duration of symptoms at the time advice was sought was seven and three-fourths months.

Five patients refused operation. In one of these cases no treatment was instituted. This patient lived for 17 months after the first symptoms. Roentgenotherapy was employed in the remaining four cases, and their

FIG. 5.—Case No. 3: Roentgenogram following removal of mandible and closure of oral fistula, nine months after operation.

average duration of life was 15.5 months, one patient living for 26 months after the lesion was first noticed. The average duration of life after onset in the entire group not operated upon (Table II) was 14 months.

The average duration of life in four patients who were operated upon but who died of recurrence was 17.7 months after appearance of first symptom and 13 months following operation. Six patients are alive and well

FIG. 6.—Case No. 3: Three months after removal of mandible, just before closure of oral fistula. Note midline position of the chin.

four years or more after operation. The average duration of life following onset of symptoms is four years and 10 months.

Ages of the patients, when first seen, ranged from 36 to 77. Three patients subjected to operation were more than 70 years old.

There were 15 males and eight females in the entire group of patients. Seven patients had adentia. Six of these had badly fitting lower dentures and were conscious of irritation of the lower gum caused by "rubbing" of the plate. The other patient (No. 9, Table I) had had adentia for 25 years and had never worn false teeth. In all of the patients in whom there were remaining teeth, dental caries were numerous and the gums were retracted and badly infected.

FIG. 7-A.—Case No. 9: Before operation.

There was one operative death (No. 5). This patient lived for 12 hours after operation and did not regain consciousness. Autopsy was not performed. This is an operative mortality rate of 8.33 per cent.

Six patients operated upon have lived for four years or longer without evidence of recurrence. This is a survival rate of 50 per cent. One other patient (No. 11), who was 74 years old when operation was performed, died in a State Hospital for mental diseases three years after operation. There was no evidence of recurrence at the time of his death. Four patients (33.3 per cent) died of recurrence of malignant disease.

Protracted external roentgenotherapy was given over the neck following operation in all cases who survived except one. The total dosage of radiation therapy employed in each case is given in Tables I and II.

Patient No. 9 was treated intensively with protracted intra-oral roentgenotherapy, administered through an intra-oral cone, before he was seen by us. The rate of growth of the neoplasm was probably influenced by this therapy but the patient was sent to this clinic by the roentgenologists who treated him because they observed evidences of continued growth. Resection of the mandible was performed but the patient ultimately died of recurrence of the growth and metastases.

Another patient (No. 18) received very intensive interstitial radiation (radon: 7680 millicurie hours) and when he was seen in the Vanderbilt University Hospital he had extensive invasion of the mandible, the floor of the mouth and the tongue, and the neck. 6900 R units of roentgenotherapy were given, and the patient died 17 months after the onset of symptoms.

SUMMARY

1. Squamous cell carcinoma of the lower gum (alveolar epithelial margin) constitutes almost one-half of malignant growths of the buccal mucosa.

2. Early erosion of the cortex of the mandible takes place and subsequent widespread invasion of the mandible occurs while the disease is still limited to a small area in the soft tissues.

3. In recent years, because of the fear of mutilating facial operations and the ease of application of radiation therapy, surgical excision of the mandible

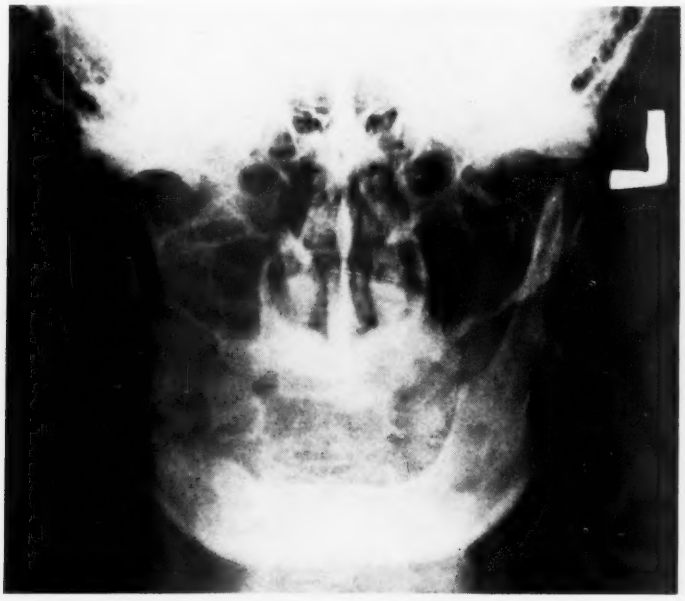

FIG. 8.—Case No. 9: Before operation. Roentgenogram showing destruction of right mandible.

FIG. 9.—Case No. 9: Eight months after operation and three months after closure of oral fistula.

has been largely abandoned in favor of radiation therapy. The treatment of squamous cell carcinoma of the gum has been disappointing, on the whole.

4. Eradication of the disease can be accomplished in a relatively large number of patients by wide, *en bloc* excision of the body of the mandible and its adjacent soft tissues.

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RATE OF EPITHELIAL REGENERATION

A CLINICAL METHOD OF MEASUREMENT, AND THE EFFECT OF VARIOUS AGENTS RECOMMENDED IN THE TREATMENT OF BURNS

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FOR some years certain members of the staff of this hospital have felt that the tanning methods in vogue for the treatment of burns are injurious to viable epithelium. The burned surfaces treated with tannic acid or various dyes have not healed as rapidly as those treated with bland ointments. This apparent delay in wound healing has remained, however, but a clinical impression. In the burned patient there are factors, other than the substance applied locally, which influence the rate of healing, and the rôle played by each may be impossible to appraise.

In the first place, the deeper the burn, the slower the healing will be. No two burned areas can be considered of identical depth or degree, and there is no proven method of judging accurately, clinically, or microscopically, the extent to which the cells are damaged by the burn. Second, complications of the burn, infection and malnutrition, delay the eventual healing. The growth of organisms on the burned surface may destroy additional cells and retard regeneration of epithelium. Acute malnutrition with loss of protein reserves may occur as the result of plasma loss and infection; an adequate protein reserve is a requisite of cellular proliferation and wound healing.[1]

The tannic acid treatment for burns was introduced by Davidson,[2] in 1928, at a time when the toxin theory of shock was popular. One of the arguments for its use was the concept that the tannic acid would coagulate, *in situ*, any tissue toxins produced in the burned cells and thus prevent or retard their absorption. Davidson felt that the tannic acid did not coagulate viable cells, but he had no objective method of measurement.

Tannic acid proved to have low bactericidal powers. Abscesses developed beneath the tannic eschar with too great frequency. In order to reduce the element of infection, Firor and Aldrich[3] recommended gentian violet. Such dyes in high concentrations produce a supple eschar and abscesses beneath are less common.* The evaluation of dyes in contrast to tannic acid has, incidentally, prompted attention to the rôle of infection in the late shock of burns.

Both tannic acid and dyes have represented improvements in the treat-

* Aldrich[4] has developed a modification of the dye treatment with his triple dyes. For bactericidal purposes, they have certain advantages over gentian violet alone.

ment of burned patients, but it must be recalled that their recent introduction† has coincided with the understanding of protein and fluid therapy. The attention of those recommending tannic acid or dyes has been so riveted on fluid loss, toxins, or infection, that they have neglected the possible noxious effect of these substances upon the viable epithelium.

Reports have recently appeared from England questioning the innocence of tannic acid[6] and the dyes.[7] In this country, Dragstedt, *et al.*,[8] and Koch,[9] among others, have advocated other methods supposedly less injurious to the viable tissues. The evidence in these reports is based either upon clinical observation, or, in the case of the dyes, upon their influence on the growth of tissue cultures. Objectively controlled measurement of the effect of tannic acid, dyes, and other substances upon the regeneration of human epithelium *in situ* is lacking.

Various substances recommended for the treatment of burned surfaces have been assayed by a simple method which judges, in the human being, the rate of healing of skin wounds. This communication presents a description of the method and the results so far obtained.

METHODS

The effect of substances upon the rate of epithelial regeneration has been measured in the human, using the donor area from which a graft of uniform thickness is cut. The donor area is subdivided into two or more portions, one of which is covered by a standard and the others by experimental preparations.

The patients used in this study required grafts of skin for various elective plastic procedures, not for burned surfaces of recent origin. The patients were healthy and otherwise normal. The diets given were adequate in protein and vitamins. No nutritional deficiencies were observed, but blood serum protein and vitamin levels were not determined. The convalescence of all patients during the hospital stay was uneventful.

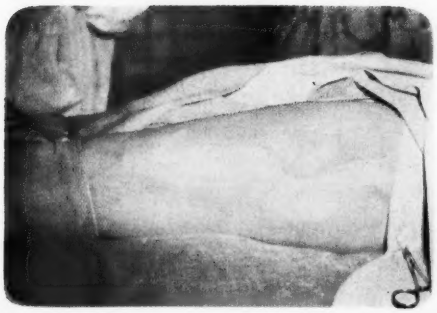
The donor site chosen was usually their lateral or medial side of the thigh, the graft being cut longitudinally. No grafts were cut transversely around the thigh, since it is considered that the skin on the inside of the thigh is not comparable to that on the outside. Occasionally the abdomen, and once the posterior surface of the lower leg, were used. The donor surface chosen was normal; it contained no scar and no previous grafts had been removed from it.

The area was shaved and washed with soap, water, and alcohol, and wrapped in a sterile towel the night preceding operation. At operation, the area was painted with three per cent iodine solution and draped.

A skin graft of uniform thickness was removed by the dermatome.[10] A standard depth of 0.012-inch was chosen. It is difficult to obtain a uniform cut with the knife set for a thinner graft. A thicker cut would penetrate

† Tannic acid was employed in Glasgow in the nineteenth century,[5] as well as in the Orient far earlier.

A



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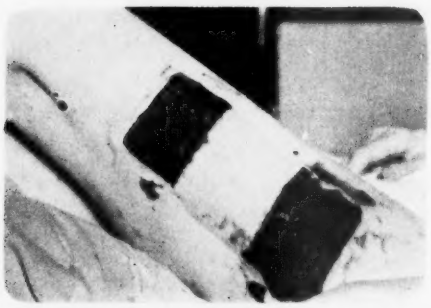

E

F

G

PLATE I.—A to G: Photographs of the donor site on the lateral aspect of the left thigh of Patient 8. The middle third of the donor site was used as the control portion and covered with boric ointment gauze. The proximal third (right side of photograph) was treated with triple dye. The distal third was treated with tannic acid. A: Skin before removal of graft. B: Donor site before application of agents. C. Fourth postoperative day. The adhesive strapping in the middle holds the boric dressing in place. D: Sixteenth postoperative day. The control area is healed. E: Twenty-sixth postoperative day. The tannic acid area is healed. F: Thirty-third postoperative day. In the triple dye area, part of the eschar is still adherent and there are several small areas not yet covered with epithelium. G: Sixty-first postoperative day. There are still unhealed portions of the triple dye area.

too deeply into the dermis, decreasing the proportion of epithelium to connective tissue in the residual dermis; healing would, therefore, involve fibrous tissue as well as epithelial regeneration.

Aerobic and anaerobic cultures of the donor area were taken immediately after removing the graft in 12 of the early cases.

A fine-mesh gauze lightly impregnated with boric acid ointment* was the standard preparation applied to the control portion of the donor area. A firm dressing was applied over the boric acid ointment gauze, anchoring it securely, and isolating it from the experimental areas. If the donor area was of sufficient length, the middle third was used as the control portion, with an experimental portion above and below it; otherwise, the area was divided into two portions.

Healing was judged to have taken place when the wound became closed, that is when the surface was covered with intact epithelium, unbreakable by the trauma of ordinary activity. The reparative process continues beyond this point, but this stage of healing was chosen because it can be ascertained clinically. It is the stage at which a dressing can first be removed without causing bleeding.

The healing of the portions of a single donor site only were compared. Even in the same patient, donor sites in different areas of the body are not necessarily similar, since the thickness of the skin differs, and although the graft removed may be of the same depth, the residual dermis and the time required for healing may differ.

Colored photographs, as records, have been taken of the donor site at operation, and at intervals during the healing period (PLATE I).

EXPERIMENTS

The donor sites of 27 patients have been used. The effect upon healing of 14 substances was compared with that of boric acid ointment; nine of these were escharotics, the others ointments. The cultures taken of the donor area at operation in 12 cases showed a scant growth of nonpathogenic bacteria in six cases.

Tannic Acid.—A ten per cent solution of tannic acid, with an approximate p_H of 2, was applied to nine cases (Table I). It was sprayed on with an atomizer, at 15-minute intervals, during the first few hours after the graft had been taken and was continued at half-hourly intervals until a firm eschar had formed. In most instances the bleeding from the raw surface continued after the first application of the tan. As this interfered with the formation of the eschar, it was gently sponged away and the spray repeated. A smooth, firm eschar resulted.

The tannic eschar was removed from 14 to 26 days after operation. In only Case 2 had healing occurred by the fourteenth day. In Case 5, the

*Boric acid ointment (boric acid, 10 per cent, in petrolatum) was chosen because it is ubiquitous, and experience suggests it to be relatively innocuous. The gauze used was No. 40- x 44-mesh.

TABLE I

Agent	Patient Number / Day on which Healing was Observed																										
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Boric acid ointment	−14	−14	13	−16	−12	−14	−11	−14	−13	9	10	10	9	−13	−13	9	10	10	9	9	10	....	14	9	9	−11	12
Tannic acid	14+	14*	22+	18+	15	14+	15	−26	15	..	....	..	..	....	....	..	....	....	....	..	..	....	..	....	..	....	..
Tannic acid and silver nitrate	14++	14*	22++	....	....	....	....	....	15	..	....	..	..	....	....	..	....	....	....	..	..	....	..	....	..	....	..
Gentian violet	....	....	....	18+	31+	....	....	....	....	..	....	..	..	....	....	..	26+	30+	....	..	..	....	..	....	..	....	..
Triple dye	....	....	....	....	....	50+	20+	61+	....	..	....	..	..	....	....	..	....	....	....	..	..	....	..	....	..	....	..
Fibrinogen, with boric acid ointment	....	....	....	....	....	....	....	....	....	9	10	10	18	....	....	9	....	....	....	..	..	....	..	....	..	....	..
dry gauze	....	....	....	....	....	....	....	....	....	13	11+	..	..	....	....	..	....	....	....	..	..	....	..	....	..	....	..
tannic acid	....	....	....	....	....	....	....	....	....	..	....	..	..	−13	−13	..	....	....	....	..	..	....	..	....	..	....	..
Triethanolamine-sulfadiazine	....	....	....	....	....	....	....	....	....	..	....	..	..	....	....	..	....	....	....	21	..	....	16	....	..	....	..
Triethanolamine-sulfadiazine, with methocel	....	....	....	....	....	....	....	....	....	..	....	..	..	....	....	..	....	....	....	..	..	....	..	11+	..	....	..
Pectinate: Nickel and silver	....	....	....	....	....	....	....	....	....	..	....	..	..	....	....	..	10	14	....	..	..	....	..	....	..	....	..
Scarlet red ointment	....	....	....	....	....	....	....	....	....	..	....	10	..	....	....	..	....	....	....	..	..	11	..	....	..	....	..
Collagen membrane	....	....	....	....	....	....	....	....	....	..	....	..	..	....	....	..	....	....	9+	..	..	....	..	....	..	....	..
Sulfadiazine ointment (U. S. Government)	....	....	....	....	....	....	....	....	....	..	....	..	..	....	....	..	....	....	....	..	..	....	..	....	9	−11	12
Sulfadiazine ointment (Dixon's)	....	....	....	....	....	....	....	....	....	..	....	..	..	....	....	..	....	....	....	..	14	38+	..	....	..	....	..

*Blood was not sponged away during tanning. The larger portion of the surface was healed at 14 days; in small areas the eschar was still adherent.

+Healing not complete on specified day; actual date of healing not determined.

−Dressing no longer adherent when first observed; healing, as defined, had occurred earlier.

surface was healed over in 15 days; the longest time required was 26 days. The controls, on the other hand, were all healed when first examined, 11 to 16 days after operation. The boric acid gauze dressing was readily removed in all these cases, and it was suspected that the healing, as defined, had occurred earlier. In subsequent cases, therefore, the boric acid dressing was examined on the ninth or tenth day, and, indeed, healing was found to have occurred by this time. A greater discrepancy in the time of healing between the control and tannic acid areas presumably exists, therefore, than that recorded in the nine experiments in this group. It is concluded that tannic acid causes a delay in epithelial regeneration.

In keeping with this conclusion is the single observation (Case 2) in which patient the blood was not sponged from the surface of the donor site as the tannic acid was applied. Healing had taken place over the larger part of the area in 14 days, but portions of the eschar were still adherent. It is felt that the blood had formed a protective layer between the wound surface and the tannic acid, and that the eschar was formed in large part, of tanned blood.

Tannic Acid and Silver Nitrate.—Tannic acid, five per cent, and silver nitrate, five per cent, were applied to donor areas in four cases, either with an atomizer or by means of cotton sponges. The application was continued at regular intervals until a firm, dry eschar was formed, usually within 24 hours. The observation about the protective effect of the blood clotting on the raw surface was made again in Case 2. When the blood was removed during tanning, healing was the same, or slower than when tannic acid alone was used. Both eschars, tannic acid alone and with silver nitrate, were removed in Cases 1 and 3 before they were free, and healing was not only behind that of the control portion but was less advanced under the silver nitrate than that beneath the tannic acid alone.

Gentian Violet.—Gentian violet, two per cent, was sprayed on to the donor area of four cases. The dye stopped the bleeding from the surface quickly and the eschar formed more rapidly than with either of the tannic acid solutions. The healing of the areas was delayed. One patient was discharged from the hospital on the eighteenth day and another on the twenty-sixth day, each with an unhealed wound. The other two patients were kept in the hospital for 30 days, and the wounds still were not healed. The control portions of the wounds healed in periods comparable with those recorded in the tannic acid experiments.

*Triple Dye.** The triple dye mixture, two per cent, used in three cases, behaved much as the gentian violet alone—bleeding was stopped and the eschar formed rapidly. One patient, Case 7, was discharged on the twentieth postoperative day, with the eschar firmly attached. The eschar of the other two patients was removed on the twenty-sixth day and, since the healing was not complete, boric acid ointment gauze was applied, and the patients

* Triple dye formula: Crystal gentian violet 3.0, brilliant green 2.0, neutral acriflavine 2.0, two per cent solution.

discharged. The wounds were not completely healed on the fiftieth and sixty-first days. The control portion was healed in one case in 11 days, and in two, in 14 days.

Fibrinogen.—A powder of human fibrinogen, thrombin, five per cent sulfadiazine, and a phosphate buffer,† was tried on nine areas. This mixture was sprayed on the donor surface with a powder blower until there was a thick frosting. The fibrinogen clotted promptly but bleeding continued beneath the clot, forming blebs. When these blebs were ruptured, uncoagulated blood escaped. Because of the continued formation of the blebs and the fragility of the coagulum, a dressing was necessary for support. In five of the areas, boric acid ointment gauze was applied as a dressing over the fibrinogen. In two other cases, a dry fine-mesh gauze was placed directly over the fibrinogen. In the remaining two areas the fibrinogen surface was tanned with a ten per cent tannic acid solution and no dressing applied.

Three of the seven control portions were healed in nine days, two, in 10 days, and two, in less than 13 days.

In four of the areas with boric acid ointment gauze over fibrinogen, healing occurred in two, in nine days, and in two, in ten days. A thin coagulum separated the gauze from the new epithelial surface. In the fifth area, healing was delayed until the eighteenth day. In the two areas on which a dry, fine-mesh gauze was placed directly over the fibrinogen, healing was retarded until the eleventh and thirteenth days. In the two areas which were tanned, the eschar formed and dried rapidly, usually in less than eight hours. The blebs of blood continued to rupture during that time. The eschar was thin and, at first, soft and flexible. Later, it contracted, curled, broke and came off in pieces. Healing had occurred in both control and experimental surfaces in the two cases, when the dressing and eschar were removed on the thirteenth day.

*Triethanolamine-Sulfadiazine (Lederle).**—Sulfadiazine, five per cent, in triethanolamine,[11] was sprayed on a portion of the donor area of two cases. In one case, healing was not complete until the twenty-first day, the control portion having healed on the ninth day. In the second case, healing was complete on the sixteenth day; the control portion was healed by the fourteenth day.

Triethanolamine-Sulfadiazine with Methocel (Lederle).—Triethanolamine-sulfadiazine with methocel was applied in one case. There was considerable difficulty in developing a firm eschar. Some maceration occurred at the junction of the control area and the area treated with the eschar. Healing of the control area was complete in nine days, and most of the area treated with the escharotic in 11 days.

Pectinates.—Various pectinates have been recommended as coatings for wound surfaces.[12] The donor site of two cases was treated with a gel of

† The fibrinogen powder was furnished for clinical evaluation by Professor Edwin J. Cohn, and his associates.

* Formula: Sulfadiazine 2.5 per cent, triethanolamine 8.0 per cent, sodium benzoate 0.2 per cent, water q.s. 100 per cent.

nickel and silver pectinate. Over each, a dry, fine-mesh gauze was applied, with a pressure dressing. Healing in one of these cases was complete on the tenth day and in the other on the fourteenth day. Both control areas were healed on the tenth day.

Scarlet Red Ointment.—Scarlet red ointment, five per cent, impregnated gauze, was used in two cases. Healing in these cases was complete on the tenth and eleventh days. Only one of these had a control area and the healing was complete on the same day.

*Collagen.**—Two sheets of pure collagen, one containing sulfadiazine, were applied to two areas in one case. Considerable blood collected beneath the pure collagen membrane, forming a crust in a few days. There was no significant bleeding beneath the collagen membrane containing the sulfadiazine. Healing of the control area and that with the collagen membrane containing the sulfadiazine was complete in nine days. The dry crust which formed beneath the pure collagen membrane became corrugated and healing of this surface was delayed.

Sulfadiazine Ointment, five per cent (Lederle—U. S. Government 175 H 14).—Sulfadiazine ointment, five per cent, made for the U. S. Government by Lederle, was used in three cases, a fine-mesh gauze being lightly impregnated with the ointment. In these cases healing occurred in 9, 11 and 12 days, respectively. The time of healing in the control areas was the same in each instance.

Sulfadiazine Ointment, five per cent (Lederle-Dixon 300 H 1194).—Dixon's ointment, with sulfadiazine, five per cent, was applied in two cases. Healing occurred in one case in 14 days; the control was healed in ten days. In the other case there was considerable maceration of the area, and healing was delayed for more than 38 days; the control area was healed in 11 days.

COMMENT

Two processes are involved in the healing of a surface wound; one is the proliferation of cells, the other contraction of the wound. The latter is accomplished by shrinkage of elastic elements in the tissues surrounding the wound and of the fibrin eschar which nature makes for such a wound. The wound created by the dermatome, set to cut a graft of uniform thickness, as described, heals primarily by cellular proliferation, with a minimum of contraction. (The area of the wound left by the dermatome remains constant during the healing). It is, therefore, a wound peculiarly suited to judging the effect of agents on epithelial growth.

The donor site is not comparable in many respects to the débrided surface of the second-degree burn. But control of the variables found in burns, such as depth of injury and infection, is so easy, using this standard wound, that it is suggested that any substance to be recommended for the local treatment of a burn should be evaluated by this simple, clinical method.

* The purified collagen was prepared by Professor F. O. Schmitt, and his associates, at the Massachusetts Institute of Technology.

In this communication are reported delays in epithelial regeneration in donor areas after the application of certain chemical agents which have been recommended in the treatment of the burned surface. Admittedly, more than the single factor of epithelial regeneration enters into the choice of an agent for the treatment of a burned surface, and no attempt is made herein to evaluate other advantages or disadvantages of the various substances.

The discrepancy in healing time between the control and experimental areas is the more significant, in view of the surprising consistency in healing time of the control areas in the various patients. Such uniformity is not to be expected in unhealthy, depleted patients, or in those with endocrine disorders. It is, therefore, to be stressed that when using this method each patient must serve as his own control, and, indeed, that a portion of the same donor area, not that of an area in another part of the body must be used for the control.

SUMMARY AND CONCLUSION

The donor area from which a skin graft of uniform thickness has been cut with the dermatome offers a simple, clinical medium for judging the effect of substances upon the healing of an epithelial wound. Various agents recommended for the treatment of a débrided burn surface have been tested by applying them to the donor areas. Tannic acid, tannic acid and silver nitrate, gentian violet, the triple dyes, and triethanolamine solutions, all have been found to delay epithelial healing as compared with the control boric acid ointment.

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INTRATHORACIC NEUROBLASTOMA

CASE REPORT

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TUMORS derived from embryonal neurogenic tissue are not uncommon in infancy and childhood. This neurogenic tissue, or sympathogonia, differentiates either into the sympathoblasts and sympathetic ganglion cells or the chromaffin cells of the adrenal medulla. Four types of tumors arise from these embryonal cells, the malignant sympathogonioma, the benign ganglioneuroma, the chromaffinoma of the adrenal medulla and the malignant neuroblastoma. The neuroblastoma is the most commonly encountered of these tumors in infancy and childhood. They vary both in size and shape from a small, smooth encapsulated mass to a large lobulated tumor and grow rapidly involving contiguous structures or metastasize through blood vessels and the lymph stream. The typical histologic appearance (Ladd and Gross[1]) show the cells in a rosette pattern, with the cytoplasm concentrated in the center of the cell and the nuclei situated in the periphery. Fine neurofibrils are in the center of the rosettes. Such a clear-cut histologic picture, however, is not always seen. The less differentiated tumors are more embryonal and more malignant. The classification on a histologic basis of these tumors has tended to create confusion in the literature.

Neuroblastomas can occur wherever sympathetic nervous tissue is present but the usual site of origin of the primary tumor is in the abdomen. Farber[2] reviewed 40 neuroblastomas in children and found 32 having an intra-abdominal origin, four were retropleural, and four cervical. The tumor may arise in the medulla of the adrenal or in any of the ganglia extending from the cervical area to the pelvis. Neuroblastomas arising in the adrenal medulla have been adequately reviewed by Redman, *et al.*,[3] while neurogenic tumors arising in the thorax have been discussed from the roentgenologic viewpoint by Kornblum and Bradshaw,[4] and Wyatt and Farber.[5] A dense, rounded shadow in the posterior portion of the chest is considered of diagnostic importance. The symptomatology of primary thoracic tumors is negligible until pressure of an enlarging tumor and evidence of metastasis become evident. The presence of an intrathoracic neuroblastoma in early infancy, without metastasis and without pressure symptoms, offers a difficult diagnostic problem, and this is especially true when the symptoms are not associated with pulmonary pathology. To overlook such a lesion is an unfortunate circumstance, as recourse to surgical intervention and roentgenotherapy (Ladd and Gross,[1] and Wyatt and Farber[5]) may give truly remarkable results.

We are reporting a case of a five-months-old infant who offered a puzzling symptomatology and who was finally diagnosed by aspiration biopsy under fluoroscopic guidance.

FIG. 1.—Liver margins as outlined by percussion.

Case Report.—Baby W. S., male, age five months, was referred, on June 18, 1941, to Dr. Gabriel Tucker at the Graduate Hospital, because of a radiopaque shadow in the lower lobe of the right lung. The baby had been apparently well until the age of three months, when he developed intermittent hyperpyrexia and began to perspire profusely, especially after feedings. On admission, the rectal temperature was 105.4° F. and later was 107.2° F. The infant was very restless and pallid. Respirations were shallow, accelerated, and dyspneic. The abdomen was markedly distended and the lower edge of the liver was below the transumbilical level (Fig. 1). There was marked suppression of breath sounds over the right lower lobe with flatness to percussion. It was felt that the child had an encapsulated process in the pleura or in the lung.

The child was given sulfathiazole, and the temperature declined by lysis. A total of 1643¾ grains of sulfathiazole was administered from June 18 to July 22.

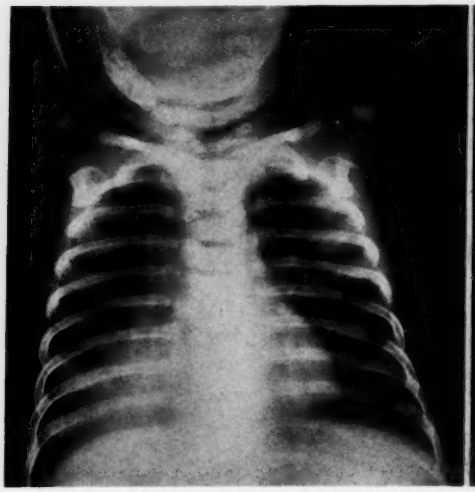

FIG. 2.—Radiogram taken preoperatively.

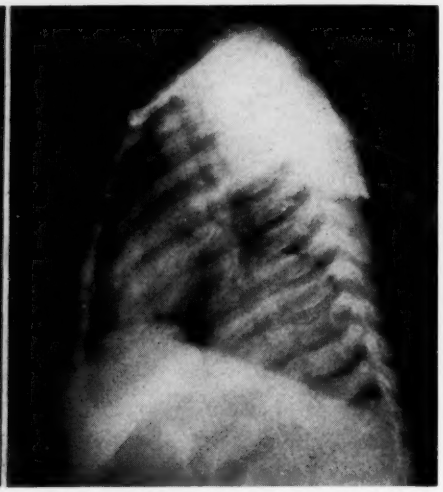

FIG. 3.—Radiogram taken preoperatively.

Roentgenologic examination, on June 18, showed: "In the examination of the chest, the bony thorax and cardiac silhouette and aorta are negative. The lung fields are also negative except for a sharply circumscribed, rounded, uniform density situated at the right base posteriorly, which is about 6 cm. in diameter. Both domes of the diaphragm move well, but the posterior mass moves very little with respiration, suggesting that it is attached to the posterior parietes. The swallowing function was negative, as tested by liquid barium. We suspect that the mass in the right lower chest is a loculated empyema." Subsequent roentgenograms (Figs. 2 and 3), on the 19th and 23rd of June, showed practically no change in the chest fields. At

this examination, congenital lung cyst, solid lung tumor, and subdiaphragmatic tumor were considered.

One uranalysis revealed glycosuria and another a heavy trace of albumin. Urinary specific gravities ranged from 1.015 to 1.030. The white count on admission was 7,150, neutrophils 68%, basophils 2%, monocytes 2%, lymphocytes 28%. Red cell count on June 19 was 4,200,000, hemoglobin, 60% (10 grams); leukocytes 10,000, neutrophils 36%, monocytes 14%, lymphocytes 50%. The baby received a transfusion of 100 cc. of blood on June 19 and 120 cc. on June 20. On June 21 the red count was 5,620,000, hemoglobin 75% (12.5 grams); leukocytes 10,000; neutrophils 82%, monocytes 6%, and lymphocytes 12%. Agglutination tests were negative. Blood sugar on July 17 was 137 mg.

FIG. 4.—Urogram taken preoperatively.

When the abdominal distension was lessened by enemas, rectal tube and prostigmin the right kidney could be felt extending below the liver but it did not appear enlarged. A subcutaneous urogram (Fig. 4) on July 8 was reported as follows: "In the films made 10, 20 and 35 minutes after subcutaneous injection of diodrast, the left kidney pelvis was well visualized and appears normal. The left ureter is not seen. The right kidney pelvis is considerably smaller and is dislocated, possibly due to rotation of the kidney. The soft tissue outline of this kidney is not definitely identified but is visualized and appears slightly larger than one would expect with such a small renal pelvis. This suggests that the kidney may be filled by neoplastic cells. In several of the films, particularly that made at 45 minutes, there is a suggestion of a soft tissue mass at the superior pole of the right kidney, and this mass may be continuous with the previously described mass extending into the lower thorax. Although these findings are not visualized with sufficient clarity to be conclusive, they, nevertheless, suggest the possibility of an adrenal tumor invading the right kidney and extending up into the lower thorax, either directly or by means of liver metastasis." A roentgenogram of the skull on July 10 revealed no evidence of metastasis. On July 15, roentgenograms of the long bones and bony thorax revealed no evidence of metastasis, and it was felt, at this time, that the mass in the chest had not increased in size.

Preoperatively, the infant had a very stormy course, accentuated by attacks of profuse perspiration, accompanied by accelerated breathing, restlessness, irritability and abdominal distension. On June 28 a biopsy specimen was obtained, under fluoroscopic guidance.

Pathologic Examination.—Microscopic: Dr. E. A. Case. "The sediment from this fluid consists mostly of blood, and the leukocytes are not numerous. Groups of cells occur, having a round, deeply stained nucleus larger than a lymphocyte and with little

or no cytoplasm. It is difficult to determine what these cells are but their appearance and arrangement suggest tumor cells but this is not certain. *Tentative Diagnosis:* Neurocytoma of the adrenal (Pepper type)."

Operation.—On July 23 it was felt that the child was in as good a condition as could possibly be hoped for, and an exploratory celiotomy was performed under ether anesthesia. The abdomen was opened in the upper right abdominal quadrant through an incision which passed along the outer edge of the right rectus muscle. The liver seemed to be perfectly normal, and upon displacing it a mass was found in the right spinal gutter. The kidney could be isolated and the adrenal could be seen very clearly. Both of these organs seemed to be normal. An opening was made through the posterior

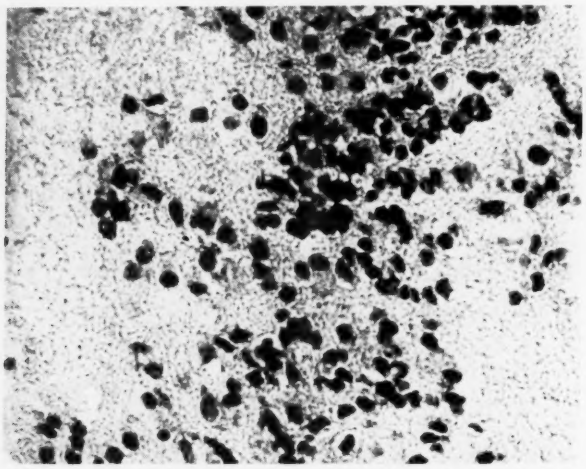

FIG. 5.—Photomicrograph of material aspirated from tumor.

parietal peritoneum and the mass which was uncovered was entirely separate from the liver. The liver was dislocated out of the abdominal cavity to the left, and it was found that the mass was not infra- but supradiaphragmatic, and it was necessary to incise the diaphragm and enter the right pleural cavity. The mass was found to be about the size of a small orange, and it corresponded to the shadow shown roentgenographically. The mass had a distinct capsule which made it possible to develop a line of cleavage and remove all of it except its hilum or pedicle, which was between two and three centimeters in width and attached to the bodies of the lower dorsal vertebrae. After clamping the pedicle, an incision was made across the tumor mass, which was then removed. This left some of the tumor behind with the pedicle. The pedicle was ligated by continuous suture ligature of No. 1 chromic catgut, and the opening in the diaphragm was closed with a continuous catgut suture, making it air-tight. The celiotomy wound was approximated by interrupted sutures of dermol. A transfusion was started during the operation. The infant was placed in an oxygen tent and, though his condition was fair at the close of the operation, he succumbed about three and one-half hours postoperatively.

An autopsy was performed, July 23, 1941, by Dr. Howard Lorenz, Resident Pathologist at the Graduate Hospital, and the pertinent facts from his report were as follows: *Thorax:* Upon opening the thorax it was first observed that the right chest cavity contained about 75 cc. of dark red blood. The right lung was fully collapsed. The left lung was well aerated. *Heart:* The pericardium was of average normal thickness, smooth and glistening. No adhesions or fluid were found in the pericardial sac. The heart weighed 55 Gm., was not enlarged, and the surface was smooth. There were no

congenital lesions such as patent foramen ovale or persistent ductus arteriosus. The diaphragm revealed an incision measuring 6 cm. long, united with sutures. *Respiratory System:* The right lung—50 Gm. The left lung—50 Gm. The right lung was collapsed, dark blue mottled. The left lung was aerated and mottled with dark and light areas. No masses felt or seen. No mediastinal lymph nodes felt. *Sympathetic Chain:* A mass of tissue, yellow-brown, soft and papillary, was found along the right paravertebral (retropleural) ganglion chain below the 10th thoracic vertebra and attachment of the diaphragm.

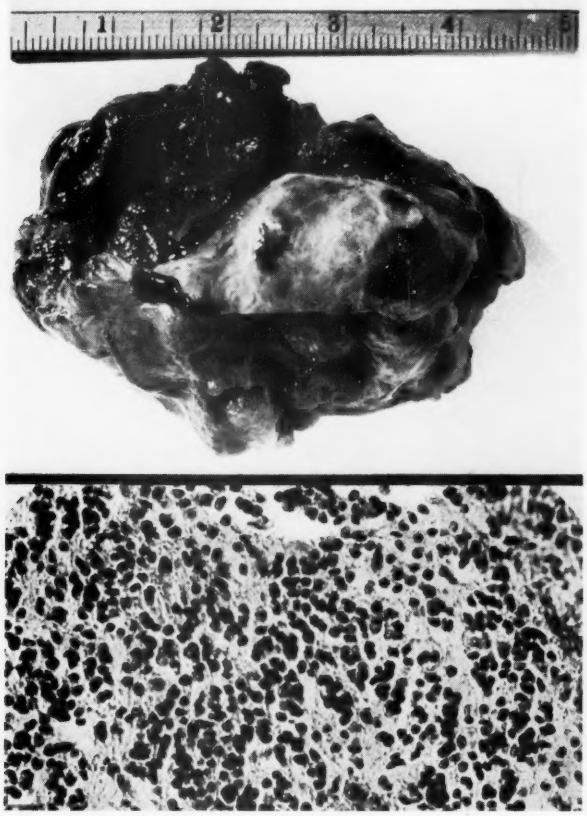

FIG. 6.—Photograph of tissue removed at operation.

FIG. 7.—Photomicrograph of section of tumor.

(This mass contained sutures). *Abdomen:* No ascites. *Gastro-intestinal Tract:* Gastro-intestinal tract was not explored in detail. *Liver:* The liver (400 Gm.) was somewhat enlarged with a smooth and homogeneous surface externally, and it cut easily. Cut surface appears homogeneous, with normal color except near the periphery in several areas, about 1 cm. wide and 0.5 cm. deep, where the color was a dark brown, almost black. Section of these areas were taken for microscopic examination. The gallbladder was bright green in color, soft, and no calculi were present. The pancreas was of moderate consistency and no masses were palpated. No evidence of necrosis was observed. The spleen weighed 25 Gm., and its capsule was wrinkled and dark. The cut surface was mottled with a sprinkling of white dots. The adrenal glands revealed no gross lesions. The right kidney (55 Gm.). Left kidney (38 Gm.) The cortex and medulla were normal in color. There was a small amount of peripelvic fat. *Gross Anatomic Diagnoses:*

1. Remains of tumor found along right paravertebral ganglion chain below 10th thoracic vertebra. 2. Collapsed right lung. 3. Right hemothorax. *Cause of Death:* Probably from hemothorax and associated shock.

Pathologic Examination.—Microscopic: Tumor. (Fig. 6) (Taken from sympathetic chain). The section (Fig. 7) shows several types of cells: (1) These have a large vesicular nucleus and very little cytoplasm, and resemble immature lymphoid cells. (2) Large eosinophilic cells with a large dark nucleus at the periphery. (3) Small lymphocytes. (4) Connective tissue cells with elongated nuclei and pink cytoplasm. (5) Here and there one sees cells which are as big as No. 2, and which stain similarly, but these have two nuclei, at the poles, with clear cytoplasm in between and in the center. In one case, it seems as if the cytoplasm had just broken in the center and two cells were formed. Rosettes are not seen. Ganglion cells are not seen. The specimen removed at operation was stained by the silver method. Many fibril-like strands are seen, which are probably connective tissue rather than nervous tissue. *Spleen:* Contains areas of hemorrhagic infiltration of pulp. *Lung:* (Right) Atelectatic. No definite evidence of metastatic tumor was found. *Adrenal Glands:* Normal. *Kidney:* Normal. *Sternum:* Shows no definite evidence of metastatic lesions. *Pathologic Diagnoses:* Tumor: Neurocytoma (atypical). Spleen: Hemorrhagic areas. Lung: Right—atelectasis; left—normal. Adrenals, kidneys, and sternum apparently normal.

SUMMARY.—Some of the cases reported have manifestations similar to those in adrenal chromaffinoma, which may be due to excessive adrenalin secretion or to "adrenergic" action, evidencing excitability, tachycardia, profuse perspiration, abdominal distension, vomiting and episodes of cardiac failure. These symptoms were quite noteworthy in this patient. Intrathoracic involvement may give either no definite physical signs or signs mimicking other types of thoracic pathology. Because of the location of the tumor in the posterior mediastinum, certain signs may arise from pressure on the lung, pleura, vertebrae, involvement of the spinal cord, and encroachment on the diaphragm and retrocardiac space. Metastatic lesions may be manifest by signs in distant regions of the body. Aspiration biopsy, under fluoroscopic guidance, would seem to be a logical procedure in some cases. In fact, it may even be beneficial, in that it may initiate hemorrhage and necrosis, with spontaneous resolution of the tumor. It has been reported that neuroblastomas may undergo hemorrhage, necrosis and spontaneous resolution, or differentiate into a benign ganglioneuroma (Ladd and Gross,[1] Cushing and Wolbach.[6]) Intrathoracic involvement may be mistaken for other types of pulmonary pathology, even with most painstaking roentgenologic studies. Once the diagnosis is definitely established, even in the presence of metastases, surgery and irradiation of the primary tumor and roentgenotherapy of the metastatic lesions is advisable. The remarkable experiences of Ladd and Gross,[1] and Wyatt and Farber[2, 5] with neuroblastomas have shown that the prognosis is not hopeless even if only a part of the tumor is removed and distant metastatic lesions are present, if deep roentgenotherapy is administered.

CONCLUSIONS

Intrathoracic neuroblastoma, without metastases, and symptoms referable to the chest, offers a difficult diagnostic problem. Aspiration biopsy is

a valuable adjunct to other diagnostic aides. Early recognition of these tumors and prompt treatment, both surgical and roentgenologic, will materially enhance the prognosis.

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EMPYEMA COMPLICATED BY BRONCHO-ESOPHAGO-PLEURAL FISTULA

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PERFORATIONS OF THE ESOPHAGUS are not uncommon. They may be due to foreign bodies, strong chemicals, carcinoma, peptic ulcer, rupture of a diverticulum, trauma, or they may occur spontaneously during severe vomiting. Such perforations may cause a mediastinitis or empyema, or both.

Perforation of an empyema into the esophagus is a rare event. According to Blauvelt[1] rib resection in the treatment of empyema was first advised by Arbuthnot Lane, in 1882. Since then, 13 cases of pleuro-esophageal fistula, with empyema, have been reported, nine cases by Blauvelt, one of which was his own. Kanter and Madoff[2] reported one case in addition to their own. Torbett and Bennett[3] reported one case of their own and one by Fonte.[4] Gott[5] reviewed 40 cases in 1933, and added four cases of spontaneous rupture. Most of these fistulae originated within the esophagus.

Zuppinger[6] reported a case of perforation of the esophagus and empyema wall by inflammation of a mediastinal lymph node due to tuberculosis. He reports similar cases by Korner, Vollcker and Verliae. The perforations were at the level of the bifurcation of the trachea and there was no associated empyema. He also mentions one case in a tuberculous child of a communication between the esophagus and trachea, which was discovered at autopsy. Three similar cases were described by Lebland, Polandt and Quincke according to this author. All were tuberculous and none had empyema. Of the 13 cases reviewed by Blauvelt, Torbett and Bennett, five died and eight recovered. In no case was closure effected surgically, although this is mentioned as a possibility by Blauvelt.

We have been unable to find a report of broncho-esophagopleural fistula either as a cause or result of empyema. The following is a report of such a case:

Case Report.—David A., white, male, age 23 months, was admitted to the James Whitcomb Riley Hospital October 6, 1941 His aunt stated that the child was desperately sick, and that everything he ate or drank drained to the outside through a tube in his chest. Also, the milk which was injected into the abdominal tube came out through the chest opening.

Past History.—The following summary is from information given by the child's aunt, and the family physician: The child was a full term baby, delivered without

complications, who weighed seven pounds at birth. His father is 27 years old, and in good health. His mother is 22 years old, and is now pregnant. There are three other children. One sister is described as being "subnormal." The patient had been apparently in good health until his present illness, which began in July, 1941, when he was 20 months old. The exact time of onset is not known but the referring physician described the early symptoms as "listlessness, fever, loss of weight and appetite." These symptoms persisted for six weeks before a physician was consulted. At this time (August, 1941) chest roentgenograms and thoracentesis revealed a massive empyema from which thick, creamy pus was aspirated. Streptococci and smaller numbers of staphylococci were identified as the causative organisms. Cultures were not made. A portion of the seventh rib was resected in the posterior axillary line and about 300 cc. of pus was evacuated. On the fourth postoperative day all food and liquids taken by mouth appeared on the chest dressings. Roentgenograms, after a weak barium mixture given by mouth, revealed an "esophageal fistula evidently communicating with the empyema cavity." Since all feedings were being lost, a gastrostomy was performed. This functioned well only if the tube was inserted into the duodenum. The boy had lost ten pounds in three months. On admission, the patient was a pale, poorly nourished child, with a temperature of 100.4° F. His weight was 18 pounds, 12 ounces. There was a draining surgical wound in the right chest, and a gastrostomy tube was in place, as previously described.

Laboratory Data.—The urine was essentially normal except for pentosuria on four occasions. Throat cultures (10/6/41 and 11/15/41) were negative for diphtheria bacilli. Blood studies showed the Kline and Mazzini tests to be negative. Hemoglobin 12.5 Gm. on admission, and ranging from 9.5 to 15 Gm. on dismissal from the hospital; R. B. C. 3,500,000, ranging from 2,200,000 to 4,000,000. W. B. C. 11,500, of which 28% were bands, 23% adult polys, 42% lymphocytes, 6% large monocytes, and 1% eosinophils, ranging from 7,250 to 25,500. In addition, basket cells, smudge cells, toxic granules, and plasma cells were reported at various times. Blood sugar 80 mg. per 100 cc. Gastric washings and throat cultures for pneumococci were negative. Culture from the chest drainage (11/20/41) showed *B. coli, Staphylococcus aureus* and hemolytic streptococci. Roentgenologic examination on admission showed increased bronchovascular markings in both lungs, with pleural thickening and fibrosis in the right base. There was no evidence of fluid or active disease in the right chest.

Course and Treatment.—On 10/14/41 lipiodol was injected into the esophagus through a catheter. This revealed tenting of the right border of the esophagus at the level of the 6th interspace with esophagobronchial fistula. At this time all food and liquid swallowed or introduced through the gastrostomy tube drained through the thoracotomy wound. A radiopaque catheter was introduced through the pylorus into the duodenum under fluoroscopic guidance. This permitted fairly satisfactory feeding through the tube. However, the catheter was either pulled out by the child or its end regurgitated by the continual vomiting, and it had to be replaced frequently.

An esophagoscopy was undertaken 10/30/41, but the fistula could not be demonstrated. The patient was in a critical condition, temperature ranged to 103.5° F. Repeated blood transfusions and intravenous injections of normal saline and glucose were given. On 12/8/41 the old thoracotomy wound was opened so that more adequate drainage could be secured. A large amount of pus was evacuated. There was some improvement following this procedure and the temperature returned to a lower level, ranging to 100° F. daily.

On February 16, 1942, iodized oil was introduced into the empyema cavity under fluoroscopic guidance. The oil was seen to communicate and to outline the bronchial

tree and esophagus (Fig. 1). This indicated a broncho-esophagopleural fistula. The fistula between the empyema cavity and esophagus was clearly seen. It formed a narrow sinus tract measuring about 2.5 cm. in length. The oil promptly entered from the distal esophagus into the cardia of the stomach. There was no evidence of cardiospasm or obstruction in the lower esophagus.

On February 24, 1942, operation was performed under ether anesthesia. An incision was made over the 8th rib. At a previous operation a portion of the 9th rib had been removed. The 8th and the remaining portion of the 9th rib were now excised. The pleura was greatly thickened. The empyema cavity was large and extended up to the 5th interspace. The child's condition was poor and it was decided to decorticate the cavity in two stages. Accordingly, the lower portion was unroofed and two lengths of one-inch Penrose drains were inserted. The skin was closed loosely about the drains. Following the operation 150 cc. of whole blood and 500 cc. of normal saline, with 5% glucose, were given intravenously. A moderately severe reaction occurred after the operation. The temperature rose to 102.5° F., and pulse to 140. By the fourth postoperative day the temperature had returned to its previous levels of 99°–100° F.

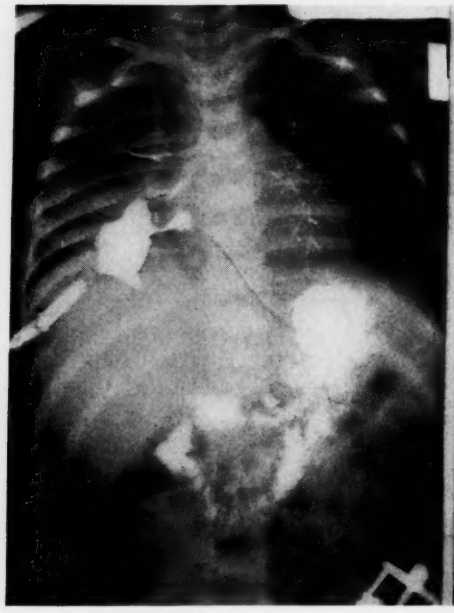

FIG. 1.—Roentgenogram showing broncho-esophagopleural fistula. Iodized oil was injected through the thoracotomy wound. (Retouched)

FIG. 2.—Roentgenogram showing esophagus after a barium meal. The fistulae are closed, and all wounds have healed. (Retouched)

Seventeen days later a transfusion of 75 cc. of whole blood was given. The second stage of the operation was performed on the following day (March 13, 1942) under ether anesthesia. A transverse incision was made over the 6th rib and a bipedicled flap of skin was elevated and retracted downward. This was done so that it would cover the large wound after granulation tissue filled the empyema cavity. The flap remained viable and prevented extensive scarring. The 6th and 7th ribs were removed

and the remainder of the thickened parietal pleura excised, thereby, completely decorticating the empyema cavity. Our exposure was excellent, and the child's condition was much better than at the previous operation. The broncho-esophageal fistula was easily identified. The esophagus was dissected loose from the bronchus by blunt and sharp dissection and the fistula closed with interruped No. 00 chromic catgut. The bronchus was dealt with in a similar manner. The cavity was packed with vaselinized gauze.

Feedings were continued through the gastrostomy tube. On March 20, 1942, another transfusion of 150 cc. of whole blood was given, and feedings were started by mouth with no leakage. The gauze packing was removed on March 22, 1942, and lightly replaced. It was removed one week later. The child was eating voraciously, and the gastrostomy tube was removed. The bronchopleural fistula was now apparent again, although the cavity was filling in very rapidly.

On May 8, 1942, the patient contracted varicella and was transferred to the isolation ward. This did not retard his progress, and the chest wound had entirely healed by June 1, 1942. His condition was excellent. There was no increase in temperature, and his weight was 25 pounds.

There remained one more task. The gastric fistula though small was persistent and annoying. The skin of the abdomen was excoriated due to the digestive action of the gastric juice. Conservative measures were unavailing. Therefore, the fistula was excised on July 14, 1942. Recovery was uneventful.

A roentgenogram of the esophagus, after a barium meal, July 30, 1942, revealed a spike-like deformity on the lateral esophageal wall in its middle third. There was no leakage, but a small amount of barium remained in the defect (Fig. 2). The meal passed readily into the stomach. The patient was discharged August 6, 1942.

Pathology.—We have considered the various ways in which this rare complication might have occurred. The possibilities may be divided under two heads: (1) Perforation of the esophagus as a *cause* of the empyema and fistulae; (2) Perforation of the esophagus as a *result* of the empyema.

(1) A suppurating mediastinal lymph node may have produced a traction diverticulum due to dense adhesions and then caused a perforation of the esophagus and bronchus. Such a condition is possible. The esophagus is apparently pulled to the right and appears to have a traction diverticulum. This supposition implies that the perforation was the cause and not the result of the empyema. It is difficult to reconcile the three-way communication by this method. An erosion connecting the esophagus and bronchus could occur, but it is difficult to explain the opening into the pleura in this manner. Because either fistula would provide an exit for the small area of suppuration delimiting further extension.

A congenital anomaly may have preceded the empyema. The trachea and esophagus are formed from the primitive foregut. Lateral grooves appear in 4–5 mm. embryos. These become deeper from below upward, finally separating the anterior trachea from the posterior esophagus. The lung bud appears as a projection of the anterior wall of the foregut in 4 mm. embryos. Before the trachea bifurcates to form the primary bronchi there appears on its right side the tracheal bud of the upper lobe of the right lung. This bronchial

bud is developed only on the right side and appears in embryos of 8–9 mm. Various types of congenital tracheo-esophageal fistula may occur. Excellent reports of these anomalies have been reported by Lanman,[7] Leven,[8] and Carter.[9] Our case may have had a thin membrane separating the esophagus from the right main stem bronchus which perforated following a pneumonia. Such a perforation would have to take place at the junction of these two structures in order for both to communicate into the pleural cavity. Although this would be a type of anomaly not previously reported, it would explain the large broncho-esophageal fistula. It would be similiar to type 3c in Lanman's classification of anomalies, but would constitute a connection of the esophagus with the right main stem bronchus instead of the trachea.

(2) The child may have had a right-sided pneumonia followed by empyema. This, in turn, was complicated by inflammation of the esophagus, ulceration or necroses and perforation. This concept does not explain the fistula into the right bronchus which communicated not only with the esophagus but with the pleural cavity as well. Furthermore, it is not likely that pus would burrow into the esophagus and then the bronchus and then connect the two. It is more in accordance with experience that, having found an outlet, as in empyema necessitatis, this would suffice especially after rib resection and open drainage.

The course of events may be as above described. The large tube introduced through the thoracotomy may have eroded through. Against this idea is the observation that the esophagus is pulled to the affected side. Since the mediastinum and its structures are very mobile in a child of this age, the esophagus would be pushed to the opposite side. Furthermore, it would have been necessary to exert continuous mesial pressure on the tube to produce this effect.

We are of the opinion that this rare group of complications is the result of at least two factors: First, some congenital anomaly of the esophagus and bronchus; and, second, an erosion through the anomalous area by the empyema.

CONCLUSION

A case of empyema complicated by broncho-esophagopleural fistula is described. It was successfully treated by stage-operations and surgical closure of the fistulae.

The author gratefully acknowledges the cooperation of Drs. Arthur P. Echternacht and John Campbell, of the X-ray Department, Indiana University Hospitals.

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SUBSTITUTION OF THE URINARY BLADDER WITH A SEGMENT OF SIGMOID

AN EXPERIMENTAL STUDY

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Total resection of the urinary bladder necessitates the provision of some method of urinary disposal. Several methods have been proposed and utilized, but all are attended by certain objectionable features. The most satisfactory method and the one employed almost exclusively is that devised by Coffey.[1] In this operation the ureters are transplanted into the sigmoid and the urine evacuated with the stools. Because the ureters open into a field which is constantly teeming with pathogenic bacteria, ascending urinary tract infections develop subsequently in a large percentage of cases, and not infrequently these infections are ultimately fatal. There are also the objectionable features of more or less frequent evacuations of liquid stools and of the psychologic effect of the loss of the act of micturition.

On the assumption that it was both possible and feasible to substitute bladder function and to use an isolated segment of the sigmoid as a substitute bladder, a two-stage operation was planned and put to experimental trial. The operation has been carried through to completion in two of the three female dogs in which it was attempted.

The technic of the operation is outlined in the illustrations in Plate I. It was performed in two stages. At the first stage the right ureter was divided at its junction with the bladder and dissected from its bed sufficiently to allow its transplantation to a loop of the sigmoid which had been selected to replace the bladder. The most proximal portion of the sigmoid which could be carried down to the position of the bladder without tension was selected. The ureter was transplanted by means of a strangulation suture at the head of a 1.5 cm. submucosal bed, as described by Coffey in his revised aseptic technic.[1] Four or five centimeters above this point the sigmoid was divided between clamps with a cautery. The distal end was closed aseptically with two rows of sutures and dropped into the pelvis. The proximal end was brought out through the wound as a temporary colostomy. The abdominal wall was closed around the exteriorized proximal end, the clamp removed, and the free edge of the bowel sutured to the skin around its circumference. Within three or four days liquid stools were passed by rectum. On the 10th postoperative day, and for four days subsequently, the blind pouch of rectum and distal sigmoid was irrigated with salt solution until the solution returned clear.

On the 14th day the second stage was performed. This consisted of the following steps: The left ureter was divided at its junction with the

bladder dissected from its bed and laid aside. The bladder was then resected and a small mushroom catheter threaded through the urethra from within out, with the mushroom-end remaining in the peritoneal cavity. The distal sigmoid was divided about three or four centimeters distal to the site of previous ureteral implantation. The mushroom-tip of the catheter was inserted into this isolated segment of sigmoid and secured within the lumen with a purse-string suture placed around it about one centimeter above the free edge. With traction applied to the catheter beyond the meatus by an assistant, the open end of the isolated pouch of sigmoid was drawn down to the cut end of the urethra and the two edges approximated with interrupted mattress sutures. The left ureter was then placed in a submucosal bed and implanted directly into the lumen of the pouch. The colostomized, or proximal end of the sigmoid was dissected free from the abdominal wall and the continuity of the bowel was reestablished by an end-

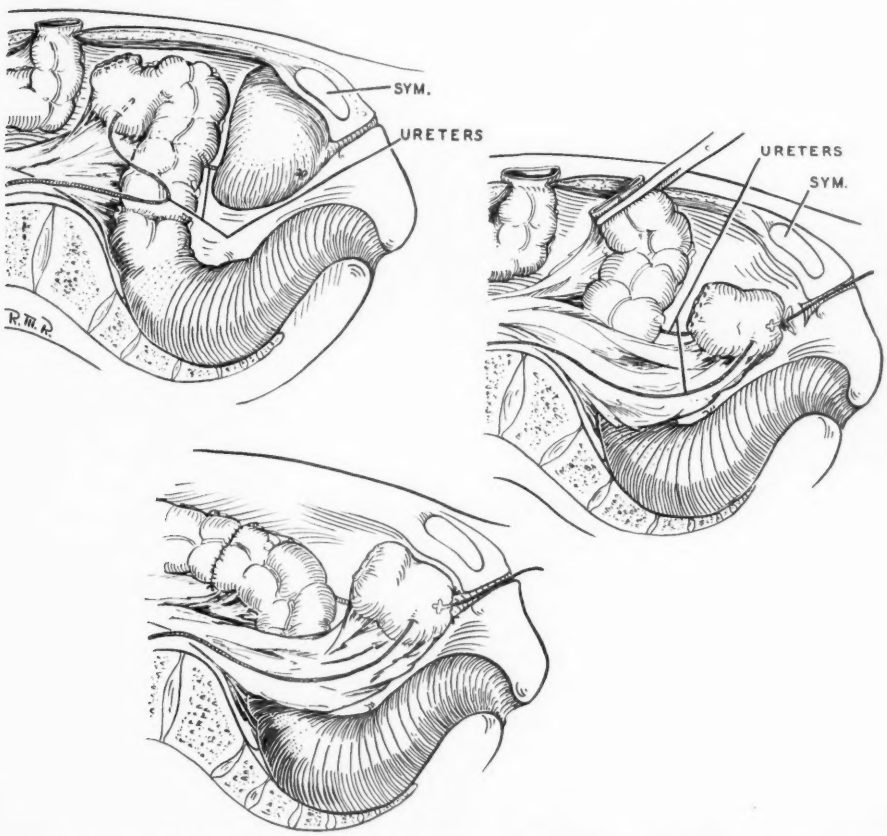

PLATE 1.—At the first stage (left) the right ureter is transplanted to the segment of the sigmoid which will subsequently be utilized as a substitute bladder. The bowel is divided above this point, the distal end infolded and the proximal end exteriorized as a colostomy.

The other two drawings show the steps of the second stage; the lower one the completed operation. These steps consist of resection of the bladder, transplantation of the left ureter, isolation of the sigmoid bladder, and suture of its distal free end to the urethra and reestablishment of continuity of the colon.

In man it would be safer to reestablish continuity of the colon by the Mikulicz's procedure. If, however, immediate direct anastomosis were performed as shown above, a vent should be provided by means of a proximal colostomy or cecostomy.

to-end anastomosis between it and the free end of the distal sigmoid. After closing the abdomen the catheter was cut off at the urethral meatus and fixed to the meatus with a suture. Five days later it was removed.

Both animals promptly developed urinary continence and, although the

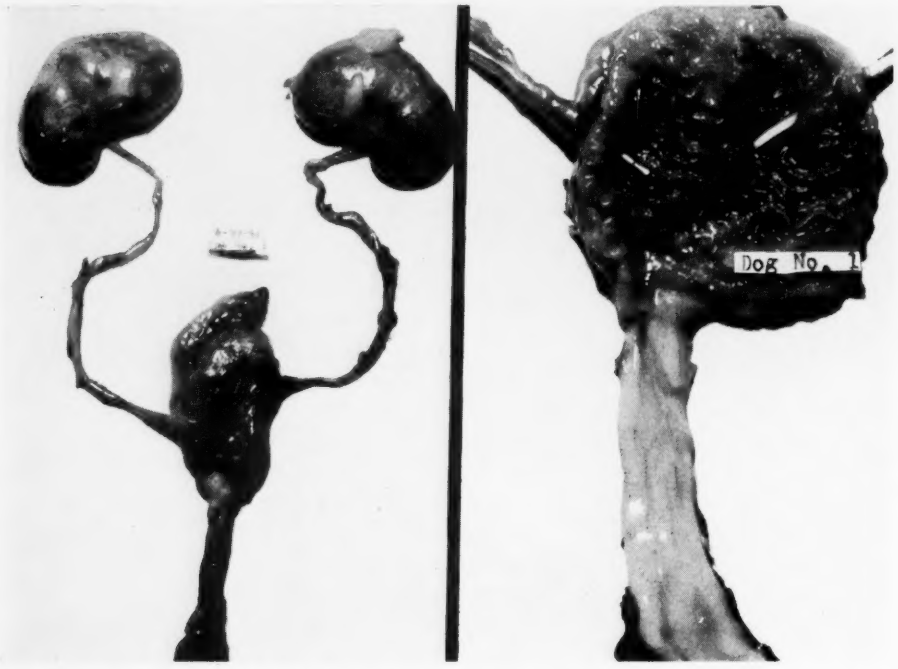

FIG. 1.—Specimen from a dog sacrificed four months after completion of the second stage. Note normal appearance of the kidneys, ureters and sigmoid bladder. Also note well healed line of fusion between the sigmoid and urethra.

sigmoid pouch would retain an installation of at least four ounces for 15 minutes or longer, it emptied so efficiently that there was always less than one-half ounce of residual urine on several determinations. Within a month after operation the urine contained only an occasional pus cell, and if white cells are a measure of infection then there was no infection up to the time that the animals were sacrificed (three months later). Apparently perfectly well, they were killed merely to obtain the specimens.

Thus, four months after the second stage of the operation the kidneys and ureters were completely normal. There was no evidence of dilatation or inflammation of either the kidney pelves or ureters. The bladder pouch did not differ from normal sigmoid. Its mucosa showed no evidence of irritation or inflammation and no metaplastic change. Photographs of the gross specimen of one animal appear in Figure 1. Bacteriologic studies of the urine and studies of motor function of the pouch are now being made.

By dividing the operation into two stages, two important objectives were accomplished. Continuous urinary excretory function was assured. The success of the first ureteral transplant was established before disturbing the

other ureter, thus avoiding the hazard of anuria. By diverting the fecal current through the temporary colostomy, and as a result of irrigations, the distal pouch was rendered relatively aseptic. This made it possible to isolate the segment of sigmoid and to carry through the rest of the operation with but slight risk of peritonitis.

CONCLUSIONS

A two-stage operation for resection of the urinary bladder and for its replacement with an isolated segment of sigmoid is presented. The operation has been performed successfully in two dogs; and by means of the sigmoid pouch normal urinary secretory and excretory functions were preserved, or rather reestablished. There was no evidence of an ascending urinary infection, but the period of observation was too short and the number of animals too few to evaluate the likelihood of this hazard.

There is no obvious reason for believing that this operation could not be utilized in man.

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SO-CALLED RETROPERITONEAL LIPOMA

REPORT OF SEVEN CASES

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SO-CALLED RETROPERITONEAL LIPOMAS comprise a rather characteristic group of tumors. In addition to fatty tissue, these neoplasms may contain connective and mucoid tissue, bone, cartilage, and sarcomatous areas. Hence, some of them are properly referred to as retroperitoneal mixed mesenchymal tumors. The etiology of "retroperitoneal lipoma" is unknown. The most common site of origin is above the pelvis in the lumbar, perirenal, or prevertebral fat. Either side of the abdominal cavity may be involved. Occasionally the tumors are multiple or bilateral. They commonly give off large projections. Growth is generally slow but progressive. So-called retroperitoneal lipomas attain the largest dimensions of any solid abdominal tumor. They may extend from diaphragm to pelvis. They are lobulated, usually yellow in color, and encapsulated. Consistency varies, with soft, fluctuant, and firm areas. Regressive and inflammatory changes are prone to develop.

On the average, "retroperitoneal lipomas" are first recognized in patients between 40 and 60 years of age. Women are affected three times as frequently as men. Diagnosis of so-called retroperitoneal lipomas before operation or autopsy is difficult. Symptoms are few and obscure. They result from enlargement of the mass, its pressure on, and displacement of adjacent organs, regressive changes and malignant proliferation. In late stages "retroperitoneal lipoma" may produce emaciation, sometimes without definite loss of weight. Physical examination and radiographic investigation are of aid in localizing a tumor. The only possible treatment is operative. Removal of the tumor, however, may be hampered by its size and relation to neighboring structures. These factors help to explain the rather high incidence of operative mortality. Recurrence follows operation not only in tumors with sarcomatous areas but also in those diagnosed as histologically benign. For this reason "retroperitoneal lipoma," regardless of the microscopic picture, is considered by some authors as potentially malignant. The effects of radiation as a pre- and postoperative measure have not yet been definitely evaluated.

In the following seven cases, we record the surgical and pathologic experience with tumors in the group of "retroperitoneal lipoma and liposarcoma" at the Buffalo General Hospital, during the past ten years.

CASE REPORTS

Case 1.—M. M., white, age 63, housewife, was admitted April 5, 1933. She died April 18, 1933. A hard lump had been noted in the lower right quadrant for three years. During the past year this lump had increased in size, with progressive enlargement of the abdomen. There was loss of weight of 16 lbs. Temperature 98–99° F.; blood pressure 160/90. Upon examination, the abdomen was enlarged, with a large, hard, nontender mass extending from costal margin to pelvis on right side. The ankles showed pitting edema.

Laboratory data.—Hemoglobin 60%; R.B.C. 3,490,000; W.B.C. 7600. Urine: Loaded with white blood cells and red blood cells.

Genito-urinary and radiographic examination: Chronic cystitis. Right catheter did not function. Upon being primed, it returned a small amount of cloudy, watery fluid with a trace of indigo carmine. Pyelogram of the right kidney showed it to be lying to the left of the spine in close proximity to the left kidney. *Clinical Impression:* Fibroid uterus.

Operation.—April 8, 1933: Avertin anesthesia. Long median incision. Enormous retroperitoneal tumor was present on the right side, extending from the ribs into pelvis, irregular in shape, more or less nodular; seemingly somewhat movable. The colon lay over the tumor, which also extended to the left side beyond the vertebrae. The upper pole of the tumor was in contact with the liver. Consistency was, for the most part, firm and hard; there were also cystic areas. The tumor could not be extirpated. Following operation the patient developed marked abdominal distention from paralytic ileus.

Postmortem findings: Retroperitoneal, lobulated, well encapsulated, lipomatous tumor, showing mucoid and edematous changes, necrosis, calcification, fibrosis, hemorrhages, and sarcomatous areas extending superiorly to right lobe of liver and inferiorly to brim of pelvis. Weight 18 pounds, measurements 33 x 20 x 10 cm.

Secondary effects of tumor: Concave depression in right lobe of liver; anteromedial displacement of colon, cecum and small intestine; dilatation of duodenum; compression of inferior vena cava, right iliac vein and artery; edema of legs; anteromedial displacement of right kidney to position opposite vertebral column, with compression atrophy of kidney; distortion of course of right ureter, with right hydronephrosis.

Other findings: Perforation of cecum; diffuse, fetid peritonitis; dilatation of small intestine; compression atelectasis of lungs; diverticulosis of colon; hypertrophic cirrhosis of liver, chronic splenic tumor; hemorrhoids; cholesterosis of gallbladder; hemorrhagic urethritis and cystitis; metropathia cystica, with small fibroid; aortic stenosis and insufficiency; hypertrophy of left ventricle.

Case 2.—C. W., white, male, age 83, was admitted November 6, 1935. He died November 21, 1935. The chief complaints were precordial pain radiating to both arms, and emesis for 1–3 days. Temperature 98–99° F.: blood pressure 110/50. Upon physical examination, the abdomen was distended with a large, nontender, immobile mass in right upper quadrant. Tympany was elicited in front of the mass. Bilateral indirect inguinal herniae were present.

Laboratory data: Hemoglobin 88%; R.B.C. 5,410,000; W.B.C. 14,000. Stools, positive test for occult blood. Urine: No remarkable data.

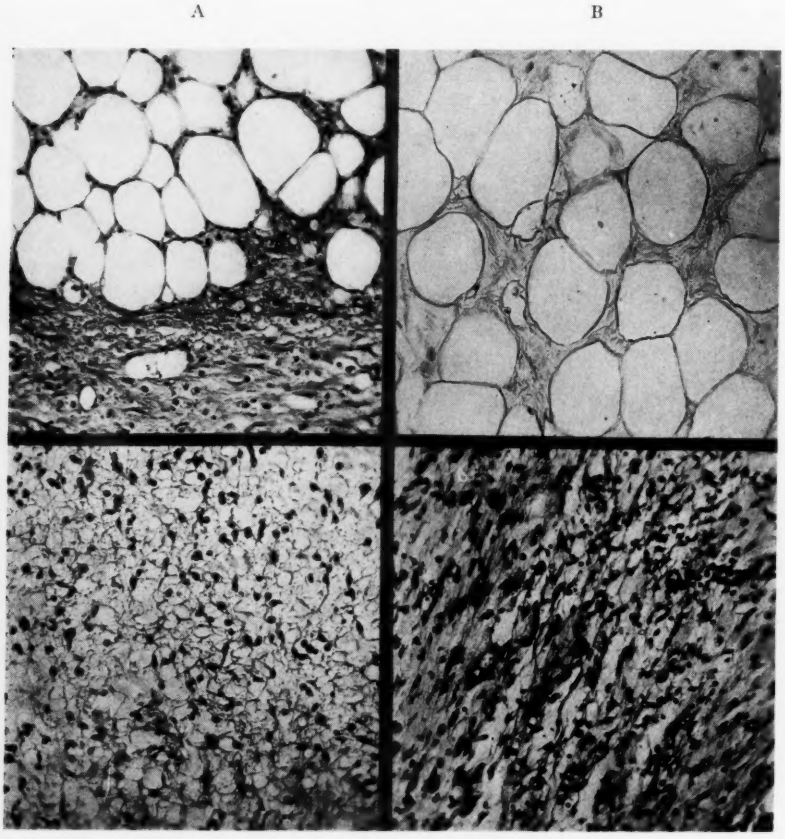
Radiographic examination: A plain film of the abdomen revealed increased density in the whole right upper quadrant. A gastro-intestinal series showed the stomach pushed to left side of abdomen, with constriction over lower portion above pylorus. There was a slight five-hour residue. The duodenum was pushed to left; its cap was irregular. An intravenous pyelogram showed the right renal pelvis at second lumbar vertebra. *Clinical Impression:* Retroperitoneal tumor.

Operation.—November 9, 1935: Avertin and novocain anesthesia. Abdominal

incision. Fatty, fibrous tumor, size of a grapefruit, was found, with origin in retroperitoneal space, firmly attached to transverse colon. Biopsy was taken. Postoperatively, patient developed mental, urinary, and respiratory symptoms.

Postmortem findings: Retroperitoneal, well encapsulated, soft lipomyxosarcoma (21 x 14 x 3 cm.) in front of right kidney firmly attached to second and third portions of duodenum, with purulent inflammation of anterior part of tumor in connection with an opening in lateral wall of third portion of duodenum.

PLATE I



A.—Fibrolipomatous structure, with hemorrhage and inflammation (Case 5).
B.—Lipomatous structure, with regressive change (Case 1).
C.—Edematous and myxomatous structure (Case 2).
D.—Sarcomatous structure (Case 3).

Other findings: Coronary sclerosis with occlusion; myocardial infarcation of left ventricle, with partial aneurysm and rupture; hematopericardium, chronic passive congestion of liver and spleen; marked lipomatosis of retroperitoneal, pelvic, pericardial and mesenteric tissue; hazelnut-sized lipoma of ascending colon; hypertrophy of prostate; hypertrophy of bladder, tracheobronchitis, fibrous, adhesive pleurisy; pulmonary emphysema.

Case 3.—V. L., white, female, age 53, was admitted August 9, 1935. She died August 14, 1935. For the past three years the abdomen had gradually increased in size. There was a loss of weight of 20 pounds. Five days before hospitalization pain

appeared in right lower quadrant. Temperature 98.6° F.: blood pressure 130/75. On physical examination, the abdomen was greatly distended. The distention was most marked in lower portion. Consistency of distended portion was soft. Percussion note over it was dull.

Laboratory data: Hemoglobin 80%, R.B.C. 4,400,000; W.B.C. 5,450. Urine: Several white blood cells. *Clinical Impression:* Ovarian cyst.

Operation.—August 10, 1935: Avertin, nitrous oxide-oxygen anesthesia. Right rectus incision. A solid, edematous tumor was found behind peritoneum on right side at level of ascending colon, extending to spleen. The tumor, which gave off about six tongue-like masses, was removed. During removal, duodenum was torn where tumor was adherent to wall of the second portion; the rent was sutured with chromic gut and linen. Terminal ileum, cecum, and colon were resected because the blood supply had been entirely removed from this portion of the intestine in excision of the tumor. The transverse colon was invaginated, purse-stringed with linen, and allowed to fall into the peritoneal cavity. Rubber tube was placed in the end of the small intestine and brought into wound. One large oilsilk pack and one large rubber tube drain were placed into tumor cavity. Transfusion. Postoperatively, patient developed fever, stupor, and respiratory symptoms.

Pathologic Examination.—Gross: Edematous, lipomatous tumor and five large masses composed of lobules. Surface of the tumor was smooth; color was yellow. Estimated weight 21 pounds; measurements 35 x 25 x 6 cm. Appendix, cecum, ascending colon, 24 cm. long. *Microscopic:* Lipofibromyxosarcoma, with edema and necrosis.

Case 4.—A. M., white, male, age 67, was admitted August 20, 1938. He died October 4, 1938. In 1935 a fatty tumor was removed from the "abdominal cavity" through a suprapubic incision; at the same time unilateral orchectomy was performed. The abdomen had become enlarged for six weeks previous to present admission. There were swelling of the legs and dyspnea. The patient said that he was getting thin, but not losing weight. Temperature 98° F.: blood pressure 120/80. Upon examination, there was emaciation. The abdomen was markedly enlarged, tense, dull. The legs were edematous.

Laboratory data: Hemoglobin 92%, R.B.C. 4,050,000; W.B.C. 6,900. Urine: Occasional white blood cell. Gastric analysis: Free hydrochloric acid present.

Radiographic examination: A plain film of the abdomen was dense. A gastrointestinal series showed a filling defect at pyloric end of the stomach. It was narrow and irregular. There was a 24-hour residue. *Roentgenologic Diagnosis*: Growth of stomach. *Clinical Impression:* Retroperitoneal tumor (aneurysm?).

Operation.—August 22, 1938: Avertin-novocain anesthesia. Right rectus incision. A retroperitoneal, football-sized, smooth, dark mass attached posteriorly was palpated. No fluid was obtained on aspiration. No murmur was heard.

Postmortem findings: Retroperitoneal myxolipoma, with edema, hemorrhage, necrosis and inflammation on right side, apparently originating in right iliac fossa; weight 20 pounds, measurement 30 cm. in diameter. In addition there were several small retroperitoneal lipomas.

Secondary effects of tumor: Displacement of stomach, small intestine and ascending colon; thrombosis of iliac veins; edema of legs; slight hydrophrosis of right kidney.

Other findings: Aspiration of gastric contents in lungs, right adhesive pleurisy, brown atrophy of heart, diverticulosis of sigmoid, leukoplakia of esophagus.

Case 5.—O. W., white, female, age 41, was admitted to the hospital January 8, 1938. She was discharged, "recovered," April 28, 1938. Ten days before hospital entry the patient developed sudden, sharp pain in left side of abdomen, which radiated into left buttock and groin. She collapsed and was very restless. The pain required morphine for relief. Temperature 101° F.: blood pressure 120/70. Upon examination, a large mass occupied entire left side of abdomen, firm, not tender, not mobile on respiration.

Laboratory data: Hemoglobin 78%, R.B.C. 4,410,000; W.B.C., 18,200. Urine: Occasional red blood cells, white blood cells, and casts. Stool: Positive test for occult blood.

Genito-urinary and radiographic examination.—January 10, 1938: On left side, catheter passed to level of twelfth dorsal vertebra toward median line of spine. It flared outward and upward in this line. Pyelogram on left showed calyces not well visualized; right kidney showed concave irregularity in lower calix (cyst?). January 13, 1938: A large elliptical-shaped density on left side, occupied space between eleventh rib and crest of ileum, from spine to periphery of abdomen. Diodrast showed left kidney crowded upward. Right kidney was well demonstrated. *Clinical Impression:* Retroperitoneal tumor.

Operation.—January 15, 1938: Avertin-nitrous oxide anesthesia. A left "T" incision. Peritoneum was separated from parietal wall. A tumor, the left kidney, and a portion of the left adrenal gland were removed. Renal vessels were controlled with chromic gut ligature. Abdomen was closed with interrupted chromic gut and silkworm sutures. Penrose drain was brought out through left flank by stab wound.

Postoperative Course: Profuse drainage from wound developed. Subsequently incision healed except at drainage site. Roentgenograms revealed sinus leading to level of first and second lumbar vertebrae.

Pathologic Examination.—Gross: Large fatty tumor, 18.5 x 13.5 x 10 cm.; estimated weight seven pounds, surrounded by a distinctly distended capsule which contained injected veins and through which showed blood masses. Kidney was firmly adherent to capsule of upper part of tumor. On section, tumor exhibited a hemorrhagic pseudocyst within the subcapsular space, most pronounced at medial surface. The pseudocyst contained fluid and clotted blood. Most of the clots were adherent to wall, which revealed hemosiderosis. Renal pelvis was not distended. Ureter was cut 5 cm. below pelvis. *Microscopic:* Typical fibrolipoma, with hemorrhage, purulent inflammation and slight necrosis. Not malignant.

Case 6.—E. P., white female, age 47, was admitted April 27, 1941. She was discharged, "recovered," May 24, 1941. Twenty years previously the patient had had a pelvic operation. During the past five years a ventral hernia had developed in the incisional scar. Temperature 99.5° F.; blood pressure 150/90. Upon examination, an incisional, reducible hernia was found in a low suprapubic midline scar. Laboratory data: Urine: 25–30 white blood cells. *Clinical Impression:* Ventral incisional hernia.

Operation.—April 29, 1941: Nitrous oxide-oxygen-ether anesthesia. Incision to left of umbilicus, over hernia. In abdomen was found a huge retroperitoneal tumor which extended from liver on right side to costal margin on left side and to pelvis. Without difficulty the whole mass was brought out of the abdominal cavity. It was found to spring from right side of pelvis. With separation of peritoneum, the tumor was enucleated from its capsule. Excess peritoneum on right side, which had covered a portion of mass, was cut away. Peritoneum was freed on each side of incision and sutured; fascia was sutured. Skin was closed with silkworm and retaining sutures of dermal.

Postoperative Course.—There was a slight amount of fetid, purulent drainage from wound. On May 13, 1941, the wound was healed.

Pathologic Examination.—Gross: Encapsulated, lipomatous tumor, with marked edema and pseudocyst formation, measurements 39 x 30 x 8 cm.; weight 16.5 pounds. *Microscopic:* Fibrolipoma, with marked edema. No recognizable evidence of malignant change.

Case 7.—R. F., white, female, age 53, was admitted December 12, 1941. She was discharged "recovered" December 29, 1941. Four years previously the patient had an hysterectomy for fibroids. One month before admission an incidental examination disclosed a mass in lower abdomen. Temperature 98.6° F.; blood pressure 200/110.

Upon examination, an orange-sized, fixed mass was palpated in right lower quadrant arising from false pelvis.

Laboratory data: R.B.C. 4,900,000; W.B.C. 11,000, with 84% neutrophils, 1% eosinophils, 9% lymphocytes and 6% monocytes. *Clinical Impression:* Ovarian cyst.

Operation.—December 14, 1941: Nitrous oxide-oxygen-ether anesthesia. Low midline incision extending up beyond the umbilicus on the right side. Masses were felt behind the peritoneum, extending from the pelvic cavity to the right kidney. Multiple lipomas were removed. They had no connection with the kidney. Right ureter was seen behind the tumors. Sulfanilamide was dusted into the retroperitoneal spaces. Opening in posterior wall was closed with plain catgut. Chromic gut was used for muscle and fascia. No drainage. Postoperative course was uneventful.

Pathologic Examination.—Gross: Lipoma consisting of several ball-shaped tumors, varying in size from 8–13 cm. in diameter. Also, conglomerated orange- and grapefruit-sized tumors connected with each other by fibrous tissue membranes. Weight of entire specimen 2,625 grams (one ovary also received). *Microscopic:* Fibrolipoma, with considerable number of atypical small giant cells and few multinucleated giant cells.

SUMMARY

The findings in our series of so-called retroperitoneal lipoma can be briefly summarized:

Age Incidence: In our seven patients the ages ranged from 41–83 years. Two patients fell into the fifth decade; two, into the sixth decade; two, into the seventh decade; and one, into the ninth decade. The average age was 58 years.

Sex Incidence: There were five females and two male.

Pathologic Findings: All the tumors were situated in the retroperitoneal tissue above the pelvis. In two cases, however, the tumor was thought to have originated in the pelvic cavity. The right side of the abdomen was involved six times. Five tumors were of the single type. In two patients, the lesion was multiple. Projections were given off from the main mass in two cases. The tumors were usually demarcated from surrounding tissue, lobulated, yellow to yellow-grey in color, and of varied consistency. Edema, pseudocyst formation, myxomatous changes, inflammation, and hemorrhage were frequent. The average weight was about 15 pounds. The largest tumor extended from diaphragm to pelvis. Tumors produced compression and displacement of liver, colon, duodenum, stomach, kidney, ureter, and inferior vena cava. Frank sarcomatous lesions were present in three cases. In two of these, which came to necropsy, metastases were not found.

Symptoms: Four patients complained of symptoms directly referable to the retroperitoneal tumor. Presence of a mass and gradual progressive enlargement of the abdomen over the period of three years was the most common complaint. In one patient, sharp pain, apparently due to subcapsular hemorrhage in the lipoma, brought the patient to a physician.

Three patients were not aware of the presence of the retroperitoneal tumor, until discovery of the lesion by a physician, who was consulted for (1) coronary occlusion; (2) incisional hernia; and (3) hypertension. Symptoms, on the basis of compression of adjacent organs by the tumor, included edema of legs, dyspnea, and vomiting. History of loss of weight

was elicited in two cases. One patient called attention to emaciation, without actual loss of weight.

Previous Operations: Three patients had celiotomies from 4–20 years before the last operation at the Buffalo General Hospital. In two of these patients the tumor had not been present at exploratory celiotomy 4 and 20 years previously; in one, a "fatty tumor" had been removed at the first operation.

Physical Examination: Five patients showed enlargement of the abdomen. Four times, a definite mass, which was not tender and did not move on respiration was palpated. Percussion note over the mass was dull or tympanitic. In two patients, with enlargement of abdomen and mass, outlines of the mass were not delineated.

Radiographic Examination: Roentgenologic studies were made in four patients. Pyelograms revealed displacement of kidney and ureter in two cases. In the other two cases, gastro-intestinal study disclosed displacement and obstruction of stomach and duodenum.

Clinical Impression: The diagnosis of "retroperitoneal lipoma" was not made preoperatively in any instance. Retroperitoneal tumor was the clinical impression in three patients; incisional hernia, in one, overian cyst in two, and fibroid uterus, in one.

Operative Reports: Six patients were operated upon *via* the transperitoneal route. The tumor could be removed in four cases. In one of these, along with the tumor, the cecum, ascending colon, and appendix had to be excised because of injury to blood supply: in another case, the kidney and portion of the adrenal had to be extirpated together with the retroperitoneal tumor. Factors which apparently influenced the operability of a tumor were size, encapsulation, and absence of incorporation with vital organs. Tumors removed, weighed 21, 7, 16.5, and 6 pounds respectively.

Mortality: Of the four patients in whom the tumor was extirpated, three recovered. Two developed drainage from the wound. The fourth patient of this group died three days after operation (excision of cecum, ascending colon, and appendix, suturing of duodenum) with fever, stupor, and respiratory symptoms. Three patients who had had celiotomies performed, but without removal of the retroperitoneal tumor, died 10–13 days following operation. The primary causes of death at autopsy were (1) peritonitis, from perforation of cecum; (2) rupture of heart from myocardial infarct, and peritoneal abscess in connection with sinus into duodenum, and (3) pulmonary aspiration of gastric content.

Irradiation: No patient received pre- or postoperative radiation.

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THE SURGICAL TREATMENT OF THE CONGENITAL MALFORMATIONS IMPLICATING THE DISTAL SPINAL CORD

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CONGENITAL ANOMALIES of the lumbosacral region comprise a variety of defects ranging from the innocent cleft of a single vertebral arch to the large meningomyelocele with absence of fusion of the neural folds and with neither mesodermal nor ectodermal covering. Some patients with such malformations come under observation because of disturbances in function of the anorectal and vesicular sphincters and/or deformities of the lower extremities, the external evidence of an underlying defect in the nervous system having passed unnoticed or being absent entirely. Others are born with an obvious mass in the lower part of the back. Since the now classical description by von Recklinghausen[1] of a case of congenital clubfoot with hypertrichosis and spina bifida occulta, a number of excellent discourses have been recorded in the literature concerning the anatomicopathologic features of these anomalies,[2, 3, 4, 5, 6] the concomitant disturbances in function of the extremities, and the alterations in neural mechanism of the vesicular and anorectal sphincters.[7, 8, 9] Many methods of therapy have been advocated for the alleviation or cure of distressing symptoms that result from the maldevelopment.[10, 11, 12, 13, 14, 15] There still remain, however, certain aspects of the therapeutic problem that have eluded satisfactory solution; consequently, many patients handicapped by lack of normal control of the urine and feces are unable to obtain desirable employment or to engage in social activities. Some of these can be rehabilitated by judicious surgery and it is with special reference to this method of treatment that the present paper is primarily concerned.

ANATOMIC AND PATHOLOGIC CONSIDERATIONS

It seems unnecessary at this time to review the recorded theories concerning the causative factors in the formation of congenital anomalies of the distal end of the spinal cord. Suffice it to say that a disturbance in the closure of the medullary folds in the embryo is quite generally held to be responsible for the maldevelopments. Normally, the neural folds in the cephalic and caudal regions are the last to close and, interestingly enough, the congenital anomalies are most commonly found in these areas. Examples are observed in which a failure in fusion of the vertebral arch or arches is the only telltale evidence that embryonal development did not travel at a normal pace. These are usually the cases of spina bifida disclosed by roentgenologic

FIG. 1.—An example of spina bifida occulta, with hypertrichosis, and an area of telangiectasia of the skin overlying a vertebral column and spinal cord malformation.

FIG. 2.—An example of spina bifida occulta, with a fibrolipomatous mass overlying the spinal defect.

examination. The presence of a dimple, a nipple, striae, telangiectasis, hypertrichosis or excessive pigmentation of the skin overlying any part of the cerebrospinal axis (Fig. 1) suggests an underlying defect. In some, there are symptoms and physical signs indicative of an accompanying disturbance referable to the nerve tissue. In others, without neurogenic dysfunction, maldevelopment of the mesoblastic elements is a prominent feature.[6] This concept is readily comprehensible, for examples are seen that show extensive overgrowth of bone about the defective area without clinical evidence that the spinal cord or cauda equina is implicated. A most remarkable instance of this type came under my observation some years ago. In this patient two

FIG. 3.—A meningomyelocele of the lumbosacral area, with the spinal cord adherent to the dome of the cyst, as illustrated in Figure 4.

parallel sheets of bone, half the width of one's palm, lying deep in the subcutaneous tissue and extending from the sacrum to the occiput, were demonstrated roentgenologically. In the cervicodorsal region there was a joint-like mechanism that permitted limited flexion and extension of the head. The child was appropriately called by the house staff, the "armadillo-kid." Often imperfections of laminae in the lumbosacral area are accompanied by adherence of the dura to the overlying tissues but without evidence of implication of the intradural structures. In others a fibrolipomatous mass may occupy the epidural space at the site of the anomaly and this mass is connected by a fibrous stalk with a large fat pad situated subcutaneously (Fig 2). Occasionally the fatty mass extends into the dural envelope and is dispersed about the spinal cord or a large filum terminale and the adjacent spinal roots. A small dorsal protrusion of the meninges may be enclosed in the fibrolipoma and this trapped within the vertebral canal.[15] If a meningocele is present, the vertebral arch or arches are widely defective and the cystic mass is covered with granulation tissue, with a parchment-like membrane, or with well-formed skin. The fluid-containing cavity in the mass may communicate freely with the subarachnoid space, or a portion of the meningocele may be composed of a compartment containing yellow fluid and not communicating with the subarachnoid space. In one instance in my experience, the mass comprised four separate cysts somewhat radially arranged about an obliterated lumen in the neck of a meningocele. Prolapse of a part of the cauda equina

into the cavity of a meningocele may be the only abnormality of the nervous system demonstrable.[16]

The most common types of congenital malformation of the lumbosacral area are the meningomyelocele and the syringomeningomyelocele (Fig. 3). As is well known, these abnormalities are frequently associated with defective developments in other parts of the neural tube, hydrocephalus being the most common. The exact relationship between these two conditions is not clearly understood. Patients with a malformation of the meningomyelocele variety usually present clinical evidence that the sacral portion of the spinal cord is functionless. This is readily understood when consideration is given to the

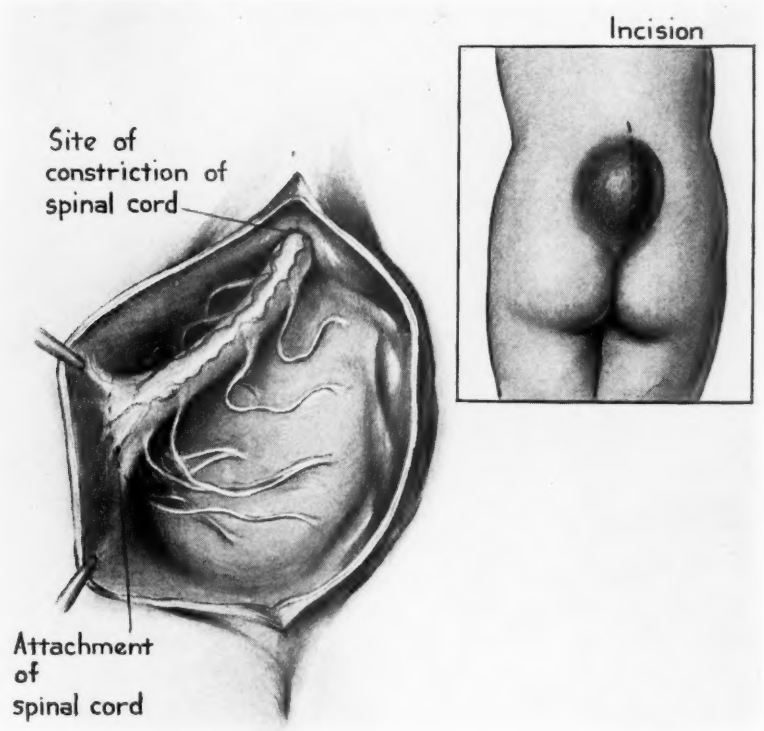

FIG. 4.—An illustration of an average example of a lumbosacral meningomyelocele as exposed at operation. The incision should be made to one side of the midline to prevent injury of the spinal cord.

gross alterations in development that are observed. In such examples, when the sac is opened at operation, there is frequently disclosed an abnormal appearing spinal cord terminating at the apex of the cavity and adherent along the dorsal cephalad portion of the cyst wall (Fig. 4). This termination of the cord is usually a somewhat fanned-out enlargement and several maldeveloped nerve radicals emerge from the mass. Distal to this there may be demonstrable a flattened-out, atrophic structure representing the remains of the coccygeal portion of the neural tube, or in some instances a part of the sacral spinal cord as well. Other variations may be observed. The

deformed spinal cord may be cystic and, if opened, a communication with an enlarged central canal is visible. Infrequently the entire meningocele is lined with the thinned-out anomalous spinal cord, the nerve roots being demonstrated only after the neural tissue has been dissected from the dura.

Microscopic examination of the spinal cord immediately cephalad to the malformation usually discloses paucity of neural cells in the grey columns, variable degrees of dilatation of the central canal, and compression of both long and short fiber tracts (Fig. 5). At the site of attachment of the cord to the sac, changes are frequently so marked as to constitute a complete transverse lesion of the cord at this level. Segments of the cord distal to its attachment to the sac show imperfect development, in fact, the neural tissue is frequently scanty and fused with mesoblastic elements.

FIG. 5.—A section of the spinal cord just cephalad to a meningomyelocele showing compression of both grey and white columns by the hydromyelia.

PHYSIOLOGIC FEATURES

The anatomic findings indicate that several features are to be given consideration in attempting to estimate the underlying reasons for functional disturbances observed clinically. One may comprehend, for the most part, at least those dependent upon gross defective development in the spinal cord. These consist, in the main, of alteration in function of the anorectal and vesicular sphincters, loss of cutaneous sensibility of the saddle area, and paresis to paralysis of the legs and feet associated with deformities of the feet and toes. Motor and sensory implication of the lower extremities depends upon the degree of neural involvement. It is to be remembered, however, that abnormal physical findings of neurogenic origin may change as the patient grows older. It has been observed in some infants with lumbosacral meningomyelocele, that for several weeks after birth the urine is passed in quantities at intervals, the diaper remaining dry in the interim. As the meningocele increases in size dribbling of urine is observed, usually an overflow incontinence, however in some cases the sphincters eventually become relaxed and total incontinence ensues.

In the normal embryo of three months the spinal cord extends the full length of the vertebral canal, but at about this time the "upward migration" of the cord begins, and at birth its distal tip has come to lie at the level of the third lumbar vertebra. The length of the vertebral canal continues to increase until full growth has been attained, without a comparable increase in the length of the spinal cord. Consequently, in adult life a normal spinal cord terminates at the lower level of the first lumbar vertebra. It seems well established that in most meningomyeloceles of the lumbosacral region, the spinal cord terminates in the dome of the sac. In many instances of so-called spina bifida occulta the termination of the cord is adherent to the meninges at the level of the bony defect in the vertebral arches. In both conditions the distal portion of the cord is so firmly anchored that upward migration does not occur. At best, there may be only slight ascent, with a reduction in size of the lumbar and sacral spinal cord to about one-half the size of the thoracic cord (giant filum terminale). The inability for the spinal cord to ascend as the vertebral canal elongates places the cord on stretch and no doubt interferes with its normal development and possibly its intrinsic blood supply. Further traction may be placed on the cord if there is a slow progressive enlargement of the sac of a meningomyelocele. Such abnormal tension is well illustrated by the Arnold-Chiari syndrome.[17] In this condition the spinal cord is fixed at a point of defective development, and as the vertebral canal increases in length the structures within the posterior cranial fossa are partly drawn through the foramen magnum into the upper cervical canal. The degree of stretching produced by a fixation of the spinal cord in the lumbosacral region is probably even greater than that observed in thoracic or cervical malformations. In all events it seems reasonable to assume that this traction can produce additional disturbances in function of the cord. In addition, a mass of abnormal mesoblastic tissue as was described under the anatomic considerations may by virtue of its size press upon the neural structures thereby producing dysfunctions of the bladder, rectum and lower extremities.

While the neurogenic changes under consideration may be caused by gross defective development of the spinal cord, traction on a maldeveloped spinal cord and/or mesoblastic malformation within the vertebral canal pressing on the neural structures, examples have been encountered in which none of these appeared to play an important part. The following is a case in point:

Case 1.—A male, age 67, had enjoyed good health with the exception of an occasional acute respiratory infection. Since birth there had been a lump over the lower part of the back. He denied any disturbance of urination or sexual function prior to onset of the present illness. About one year before admission to the hospital there was noted slight difficulty of urination. This disturbance became progressively worse and three months before entry he resorted to the use of a catheter. A genito-urinary specialist was consulted who failed to find hypertrophy of the prostrate gland or other causes of urethral obstruction. The examination disclosed no abnormalities except those related to a congenital anomaly of the lumbosacral region. There was a

rounded, soft prominence over the distal part of the spine covered with well developed skin. The third, fourth and fifth sacral dermatomic zones were anaesthetic and analgesic. The external anal sphincter was relaxed. The ankle jerks were absent bilaterally. At operation, the major part of the mass was found to be composed of fat with irregularly disposed heavy bands of fibrous tissue. The fifth lumbar and first sacral vertebral arches were bifid. In the central part of the mass, and protruding through the bony cleft, was a multicystic malformation in which an abnormal spinal cord terminated (Fig. 6). The defective spinal cord was divided at its termination in the mass, the cord replaced in vertebral canal, the dural envelope reconstructed, and the wound closed with silk. The postoperative course was uneventful. Three months after operation recovery was complete and normal control of the bladder and rectum has continued during the past six years.

FIG. 6.—A fibrolipomatous mass, with an enclosed malformation of the distal part of the spinal cord removed at operation.

Comment.—The appearance of the spinal cord above the area implicated presented evidence that a normal upward migration had not occurred. The size of the fibrolipomatous mass and the cystic formation found in the vertebral canal was not such that one could assume that a direct compression of the neural elements was the causative factor of the dysfunction. It seemed unlikely that traction on the cord could account for the onset of symptoms at this late period in life. An etiologic agent could, therefore, not be assigned with certainty.

The physiology of both micturition and defecation is still not clearly understood, although some excellent work has been reported on the subject.[18, 19, 20, 21] It seems well substantiated that the internal vesicular sphincter contracts and relaxes in reciprocal relationship with the detrusor muscle. Since the exact rôle of the three components (sympathetic, parasympathetic and somatic) of the neural mechanism of the bladder in normal man is as

yet in some doubt, it is unwise to assign to each of them a particular function in disease. In an attempt to approach the problem from a clinical viewpoint, cystometric studies have been reported that appear to offer some help in estimating the exact type of pathophysiologic alterations encountered in examples of lumbosacral spina bifida.[7, 18] McCarroll states that by careful cystometric studies all bladders can be classified according to the status of the two involuntary muscle components and of the voluntary sphincter. Such examination (cystometric) necessitates the introduction of a catheter into the urinary bladder, a procedure that is all too frequently followed by infection. The method is not applicable before the fifth to sixth year of life since cooperation of the patient is a requisite. Furthermore, it is in this younger age-group that surgical treatment frequently becomes mandatory. Therefore, an estimation of the function of the urinary bladder by other methods seems advisable. Useful information can be obtained regarding the function of the bladder by roentgenologic studies following the intravenous or subcutaneous injection of diodrast or comparable contrast media that is excreted by the kidneys.

The physiology of the bladder in any patient with urinary disturbance due to a developmental defect of the distal spinal cord may be determined by (1) observation relative to dribbling of urine: (2) the quantity of urine passed at each automatic involuntary voiding; (3) the frequency of urination; (4) an estimation of the residual urine after automatic voiding or following voluntary emptying of the bladder; and (5) the contour of the bladder before and after partial emptying. The first three of these may be readily determined, however, the last two require the intravenous or subcutaneous injection of a contrast medium that is excreted by the kidneys and the taking of roentgenograms of the urinary bladder at 15- to 20-minute intervals for a period of two hours or until urine has been passed. An additional study should be carried out immediately after automatic involuntary voiding, emptying by straining, or during overflow dribbling, both anteroposterior and lateral views being made for a record of the contour of the bladder.

CLINICAL FINDINGS

As would be expected from the anatomic description of the congenital anomalies that have been observed, no two examples are identical in their clinical manifestations. There are (a) spina bifida occulta without neural involvement; (b) spina bifida occulta with neural dysfunction; (c) spina bifida and meningocele without neural implication; and (d) spina bifida and meningocele with neural implication, or more broadly stated, spina bifida with and without myelodysplasia. Although some patients may present cutaneous evidence (hypertrichosis, telangiectasis, a dimple, *etc.*) that the underlying tissues are anomalous, most instances of so-called spina bifida occulta have been incidentally disclosed roentgenologically. Others with or without cutaneous markings and with roentgenographic evidence of a bifid state of the last lumbar and/or first sacral vertebral arch, may have symptoms (especially disturbances in micturition) that have persisted since infancy.

Occasionally symptoms have been present during childhood, then disappeared, only to recur after a number of years. Finally, there may be no complaint until the fifth or sixth decade when a slight disturbance of the urinary apparatus results in urinary retention. Some patients have mild alterations in function of the distal spinal cord throughout an active and useful life and it is only following the introduction of a diagnostic instrument into the urinary bladder or the ill-advised use of a catheter, that a chain of symptoms is initiated which frequently persists. The following report is an illustration:

Case 2.—A female, age 29, with a rounded elevation over the lumbosacral area covered with true skin, had observed since childhood that it was necessary to strain moderately to start the urinary flow. On several occasions when accidentally struck in the lower back she had "lost her water." In addition, the bowels were costive and the right foot was slightly deformed. Nevertheless, she had engaged in social activities, and for a number of years gone to business. She was married at age 24, and had had a child. For two days following delivery, there was urinary retention, relieved by catheterization. Voluntary urination was then reestablished and she was "normal" again. Following the birth of a second child, the urine was intermittently withdrawn by catheter for a period of three days, after which normal micturition was again established. This time she did not fare so fortunately. There ensued chills and fever, later intermittent retention of purulent urine and suprapubic pain. Bladder irrigations were instituted with some relief but before long there was another episode of chills and fever associated with dull aching pains in the right flank and right kidney region. It became increasingly more difficult for her to pass urine, requiring much straining even to partially empty the bladder. This patient is still in serious difficulty from the urinary tract infection, 18 months after the birth of her second child.

Comment.—The method of emptying the urinary bladder by suprapubic pressure is apparently not generally known or at least seldom employed. It should be used in all instances of urinary retention due to neural dysfunction and catheterization should not be resorted to except as a last resort. Once a pyogenic micro-organism has established itself in the urinary tract the conditions are favorable for continued growth of the bacteria in spite of all therapeutic measures.

Russell Brain[22] has commented on the patient that comes under observation during adult life as follows: "In such cases (spina bifida occulta) a careful investigation of the history usually shows that symptoms were present at an early age, though improvement may have occurred, to be followed by a relapse in early adult life. Such a relapse may be due to the effect of growth in causing tension upon the lower end of the cord and cauda equina, which are anchored at an abnormally low level or to the compression of these structures by fat or by the band described by Leri." In all instances of congenital anomalies of the spinal cord encountered in adult life, especially if symptoms have been absent for several years and then reappeared, one must be on guard lest a more recently established lesion of the urinary apparatus or spinal cord be overlooked.

While the diagnosis of spina bifida occulta may be arrived at without difficulty, it is sometimes impossible to determine the exact part the anomaly may play in a child without evidence of dysfunction other than nocturnal

enuresis. Frequently bed-wetting is the only manifestation, the child being continent during the day. In all such cases conservative therapeutic measures are to be given a fair trial before any form of operative interference is carried out.

Another group of the malformations of the lumbosacral region are those with obvious protruding cystic masses covered with a thin bluish layer of epidermis or a reddish granular surface consisting of a malformed spinal cord without cutaneous protection. Usually the surface of the latter is weeping cerebrospinal fluid. The lower extremities of patients with this type of lesion are commonly distorted and the musculature of the legs and feet paretic or paralyzed. Analgesia and anesthesia of the buttocks, lateral aspects of the legs, and the feet may be demonstrable. The ankle jerks are absent. The external anal sphincter is frequently patulous. During forceful crying urine and feces may be extruded. Ventriculographic studies will frequently disclose considerable ventricular dilatation. Some of these patients require surgical repair of the spinal defect during the first few months of life lest the thin membrane of epidermis rupture and infection ensue. Furthermore, the cystic mass if untreated increases in size, thereby placing additional traction on the intradural structures. If the meningomyelocele be well protected by relatively heavy covering, operation may be deferred until the child is ten to twelve months of age.

DISCUSSION RELATIVE TO THERAPY

In contemplating operation it is to be remembered that conservative measures are frequently ineffective and that spontaneous cures are practically never observed. The pertinent information derived from all available sources (studies of specimens obtained at autopsy, reports of observations made at operation, and theoretic concepts based on clinical findings) indicates three important factors acting singly or in combination that should be given consideration in evaluating the cause of the dysfunction associated with congenital malformations of the distal end of the spinal cord. These are (a) abnormal masses of mesodermal tissue that press upon the neural structures; (b) defective development of the sacral spinal cord itself; and (c) absence of upward migration of the spinal cord with resulting neural dysfunction dependent upon an abnormal tension being exerted on the cord. It is this traction on the spinal cord that has not been accorded its due consideration in discussions of the surgical treatment of spina bifida occulta and of the more obvious congenital malformations of the lumbosacral region.

In all instances it becomes necessary to differentiate the dribbling of urine due to a relaxed sphincter from that due to overflow incontinence, in estimating the amount of residual urine, and in determining the contour of the urinary bladder. These are basic features that must be evaluated before instituting surgical treatment in a patient with spina bifida with myeleodysplasia.

There appears to be little diversity of opinion regarding the surgical treatment of simple meningoceles. These lesions are relatively rare in the

lumbosacral region. Examples have been observed at operation in which the neck of the sac was rather small and its lumen sometimes completely obliterated, there being no obvious communication between the cavity of the mass and the spinal subarachnoid space. Following careful inspection of the interior of the cyst, total excision of the meningocele will not be followed by hydrocephalus in the majority of instances. Treating the sac by rolling it up and covering the mass with a tent of fascia, as advocated by Penfield and Cone,[11] has not decreased the possibility of augmentation of ventricular hydrops in my experience. Masses of adipose tissue, the so-

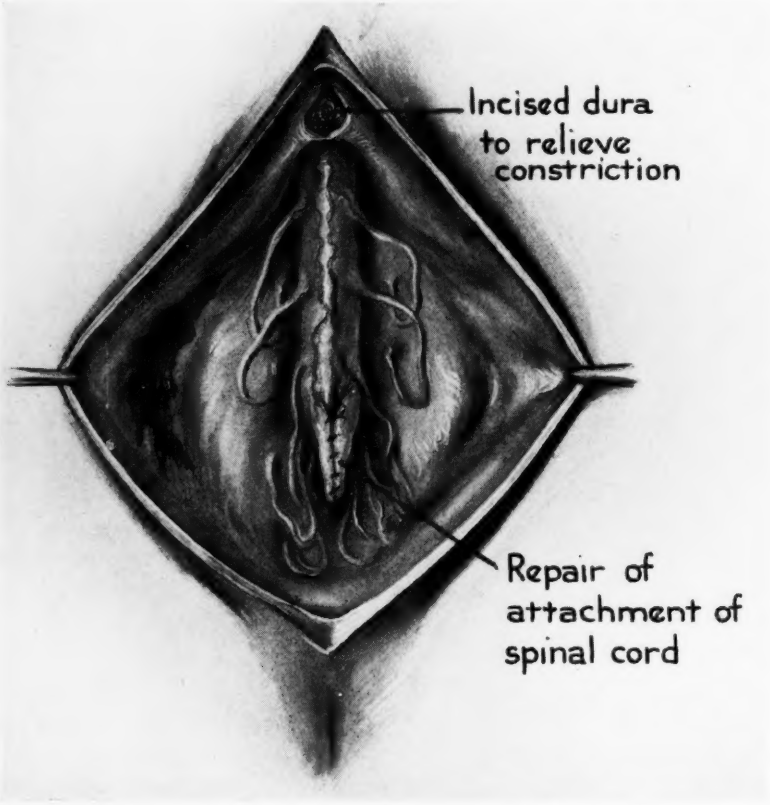

FIG. 7—Illustrating the appearance of the operative field after the spinal cord has been detached from the dome of the cyst wall.

called fibrolipomata, and the "blind" meningoceles are to be well exposed and completely removed except for the fat through which spinal nerves may pass as they leave an abnormally short dural cul-de-sac.

The selection of a patient who may be improved by operative intervention is sometimes difficult. Certainly, one should not expect to correct total relaxation of the anorectal and vesicular sphincters associated with grave disorder in both motor and sensory function of the lower extremities by an operation upon a malformed spinal cord. If operation is to be carried out under these conditions it should be understood that the unsightly mass

is to be removed, so that danger of spontaneous rupture is eliminated but that the neural dysfunction will probably remain unaltered. If there be minimal motor and sensory disturbances in the legs and feet associated with analgesia and anesthesia of the saddle-area, and a spastic state of the internal sphincters, improvement in function of the sphincters, in particular, usually follows operative intervention. This has been obtained in both spina bifida occulta, where the spinal cord is adherent to the abnormal dura as well as in the meningomyeloceles. The spinal cord distal to the point of its adherence and the nerves attached thereto are usually functionless. For this

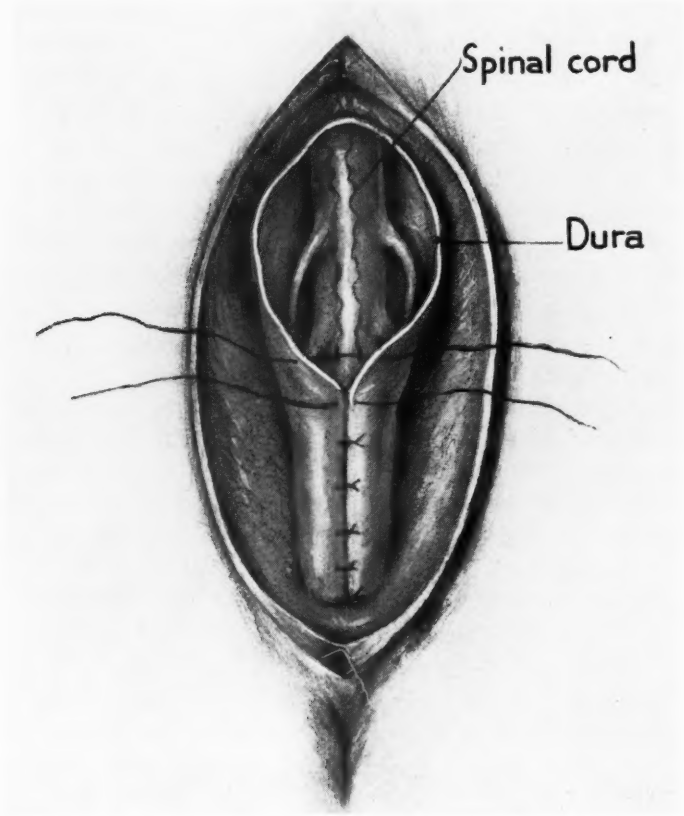

FIG. 8.—The spinal cord is lying free in the vertebral canal and a dural envelope is being reconstructed.

reason it becomes useless to attempt preservation of these structures, however, great care should be exercised to prevent damage to nerve tissue at, or cephalad to, the point of the spinal cord attachment. The incision for the exposure of the lesion should be made slightly to the side of the midline, thereby obviating possible damage to the spinal cord at its point of attachment (Fig. 4). This is particularly important in opening the cystic portion of a meningomyelocele. After adequate exposure and identification of all structures the cord should be freed and the cut surface closed by approximating the edges of the pia mater (Fig. 7). The cord may be found constricted

at its entrance to the sac. If so, the dura should be incised in order to relieve the constriction and a plastic repair performed to insure against recurrence of the strangulation at this site. A loose-fitting dural envelope is reconstructed, the redundant part of the sac excised and the wound closed with layer silk (Fig. 8).

Operations upon children less than 18 months of age should be performed under local infiltration of novocain. In older children and adult patients open drop ether has been employed, however, other types of inhalation anesthesia may prove just as satisfactory. The operation should be conducted with the head at a lower level than the operative field to prevent excessive loss of cerebrospinal fluid. This requirement is best met in small children by making the subject fast to a board and tilting the foot end upward. For older children and adults the operating table may be tilted to the desired position. Another item that assumes considerable importance is the prevention of contamination of the wound or the sterile drapes with feces. This is especially true in young children when the operation is being performed under local anesthesia, and the child is frequently crying. Because of disturbance in function of the anorectal sphincters fecal material is frequently extruded regardless of the care exercised in the preoperative preparation. To prevent this the anal canal is packed with cotton and the gluteal masses strapped together with adhesive tape. In addition the knees should be fixed in a fashion to keep the thighs apart. If feces is extruded it will be retained in the space between the thighs and not forced into the operative field or contaminate the drapes. At the completion of the operation in either children or adults the wound is sealed with a collodion dressing. During the postoperative period the patient should be kept on the abdomen or on the side. A cradle is placed to support the bed clothing, and diapers should not be used. The feedings need not be altered from the preoperative routine if the operation has been performed under local anesthesia. If there is evidence of increased intracranial tension this may be reduced by ventricular or cisternal puncture according to indication. Great care must be employed when introducing a needle into the cisterna magna since in some cases the medulla may have been drawn into the foramen magnum by the traction on the spinal cord and the cisterna magna thereby partially obliterated.

In the instances in which improvement in the function of the anorectal and vesicular sphincters is not obtained by the operative procedure herein described, excision of the superior hypogastric plexus should be given consideration. If all methods have failed to control the urinary and fecal incontinence and the sphincters are totally relaxed, artificial sphincters may be provided by the transplantation of the gracilis muscle.[23]

RESULTS

During the past ten years 104 cases of congenital maldevelopment of the spinal cord and its coverings have been treated. In 31 of these the lesions were located in the lumbosacral region and implicated the distal part of the

spinal cord. Seventeen of these 31 patients were considered to have defects that would lend themselves to surgical treatment. There were five adults and 12 children that were subjected to operation. The oldest was age 67, and the youngest an infant of ten days. Good results were obtained in eight patients by freeing the spinal cord, as herein advocated; improvement was observed in three; one patient died of meningitis following operation, four showed no permanent changes attributable to the operation; and the remaining one could not be followed. One of the four patients, an adult considered as a failure, showed some improvement for six months after operation only to have a return of the preoperative difficulties in controlling the urine and feces. Two of the three listed as improved continue to have nocturnal enuresis although capable of controlling the urine during the day.

Among the eight patients in whom the results were considered satisfactory there were five who acquired complete voluntary control of the urine and feces after operation. Two of the remaining three resort to moderate straining to initiate urinary flow. The other one, a boy age four, who was operated upon two years ago, likewise, has some difficulty in initiating urination but has shown favorable progress during the past year. The improvement in the function of the legs and feet has not been as dramatic as the changes brought about in the control of the anorectal and vesicular sphincters. The same may be said for the analgesia and anesthesia of the saddle-area. There have been demonstrable changes for the better but no instance of complete recovery of these involved regions. It is impossible to predict with certainty at operation what the postoperative result will be, however, it may be said that the more distal the involvement of the spinal cord the better the chances for restoration of sphincteric control.

CONCLUSIONS

In a consideration of the dysfunctions attending the congenital malformation of the distal end of the spinal cord, three important factors have been discussed: First, the disturbances produced by fibrolipomatous masses encased in the vertebral canal and exerting pressure on the adjacent neural structures; second, the lack of development of the spinal cord itself; and, third, the failure of normal upward migration of the spinal cord due to adherence of the terminal part of the cord at the site of the congenital anomaly, with a resultant abnormal tension on the cord as the normal growth of the vertebral column continues. It is comprehensible how the first and second of these etiologic factors may affect voluntary control of the anorectal and vesicular sphincters and the function of the legs and feet. There are some features concerning the third factor that are not clearly understood, however, in some patients of the present series the surgical liberation of the adherent spinal cord has resulted in improvement. The operation has been described and the major steps in its technical execution illustrated. Following detachment of the spinal cord and the reconstruction of the dural envelope the resultant improvement can perhaps logically be attributed to the release of a taut cord.

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DISCUSSION.—DR. IRA COHEN (New York) expressed some surprise that out of a total of 104 cases of congenital anomalies less than one-half were in the lumbosacral region. He would have supposed that more than half would be in this location. The more common type of spina bifida is that seen in the infant, with the sac so thin that one is almost afraid that a breath will rupture it. In such a case the fear of a rupture and the development of meningitis stares the surgeon in the face, on the one hand, and, on the other hand, there is his deep desire to postpone operation, if it should be operated upon at all. This type of case presents no diagnostic problem but does offer one as to when to operate, if to operate, and exactly what type of operation should be undertaken. At times, the surgeon is forced to operate to save life. When there

seems to be a complete paraplegia, with a rectal sphincter which is obviously not under any control (it is a little more difficult to tell about the urethral sphincter), it is fair then to let the parents share the responsibility in deciding whether an operation should be performed. As to the character of the operation, Doctor Browder may be correct in his statement that excision of the sac in no way influences the future development of hydrocephalus. Dorothy Russell has reported ten consecutive cases of meningomyocele that came to operation, and in all there was found, at that early stage, a medulla which was crowded down into the foramen magnum and there was beginning hydrocephalus. The question must also arise as to (1) whether in addition to the hydrocephalus there is not already present at that time a deformity at the upper end of the spinal canal not necessarily due to traction, and that no matter what may be done at the lower end the patient will go on and develop hydrocephalus; or (2) should one take the stand, as Doctor Penfield does, that the sac is partly an absorbing membrane, and that in the sacrifice of this sac, rather than enfolding it, the spinal fluid circulation becomes so thrown out of adjustment that hydrocephalus will surely develop.

The other group—the spina bifida occulta—presents not so much a problem in therapy as in diagnosis. In 1918, the late Dr. Walter M. Brickner wrote a very interesting paper on the subject, presenting ten cases, five of whom had been operated upon by him. The presenting symptom in many of the cases being trophic ulceration of the extremities. Doctor Brickner brought out the point that trophic disturbances of the extremities, which are not readily explained otherwise, should lead one to think of at least the possibility of a spina bifida occulta.

Dr. Bronson S. Ray (New York) said that what may prove, in rare cases, to be the most important factor of all, is edema of the lower end of the cord at some fixed point. It is to be hoped, upon theoretic grounds, if not on the basis of experience, that in some individuals the release of this attachment alone might serve a very good purpose. As to the question of sacrificing or preserving the sac in a meningomyelocele, Doctor Ray's experience has been very much that of Doctor Browder.

Dr. Jefferson Browder (closing) said that with regard to the relative frequency of anomalies in the lumbosacral region, he had excluded instances of meningomyelocele that occurred in the lumbar area without implication of the sacral region. The important feature of the operation for congenital anomalies implicating the distal part of the spinal cord is the release of the cord. To be sure, this is purely a theoretic concept, but Doctor Browder thought that restoration of function might be attributed to this particular operative maneuver.

THE TREATMENT OF CONGENITAL HEMANGIOMATA OF THE SKIN

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IT is generally believed that simple hemangiomata are essentially congenital in nature. They probably have their origin, according to Watson and McCarthy,[1] in embryonic sequestrations of mesodermal tissue and grow by projecting buds of endothelial tissue.

Hemangiomata vary greatly in structure and the various types demand greatly varying types of treatment. A rigid classification is almost impossible but they may be divided into groups which overlap to a certain extent. Watson and McCarthy classify them as follows: (1) Capillary hemangioma; (2) cavernous hemangioma; (3) angioblastic or hypertrophic hemangioma; (4) racemose hemangioma; (5) diffuse systemic hemangioma; (6) metastasizing hemangioma; (7) nevus venosus or port wine stain; and (8) hereditary hemorrhagic telangiectasis.

A B

FIG. 1.—Case 1: A. Before treatment. B. After treatment.

The capillary and cavernous hemangioma and the port wine stains are by far the most frequent types. The material presented in this communication will deal with the first two types exclusively, or more correctly with capillary hemangiomata and those hemangiomata which exhibit characteristics of both types. The essential difference in these two types is in the size

of the blood spaces. Most of the deeply placed hemangioma are cavernous in type. Most of those involving the skin are essentially capillary but may be partially cavernous in type. Capillary hemangiomata are more truly neoplastic in character, they grow more rapidly and may more correctly be called hemangio-endothelioma. It is to be expected, therefore, that they be more sensitive to radiation therapy. This type of therapy when applied to the more cavernous types is essentially sclerosing in nature.

It has been pointed out by Brown and Byars,[2] Watson and McCarthy, and Ward and Covington[3] that congenital capillary or cavernous hemangioma

A B

FIG. 2.—Case 2: A. Before treatment. B. After treatment.

occur frequently on the head and neck and frequently involve areas where the cosmetic result of treatment is extremely important. It has also been pointed out by the above mentioned writers, and others, that these tumors may be satisfactorily treated by a number of methods with equally good results as far as curing the lesion is concerned. These methods include surgical excision, destruction by cauterization or desiccation, the use of carbon dioxide snow, the injection of sclerosing solutions, and treatment by some form of radiation. However, the results obtained by these methods may vary greatly from the cosmetic standpoint.

In those regions where excision of tissue would necessitate extensive and difficult plastic repair or where extensive scarring due to various forms of destruction would cause deformity, radiation therapy has been extensively used. This may be accomplished by the use of roentgenotherapy, the surface application of radium or radon, or the interstitial application of needles containing radium or radon seeds. Brown and Byars have emphasized the excellent results to be obtained from the use of radon seeds and also the convenience and lack of danger of the method.

The material presented herein is confined to this type of treatment alone. A series of cases is presented showing the results obtained by this method.

The technic advised by Brown and Byars has been followed as far as possible, using one radon seed for roughly each cubic centimeter of tissue irradiated, and the content of each seed varying from 0.25 to 1.0 millicurie. The amount of radon per seed depends on the size and location of the tumor. The 0.25 and 0.5 millicurie seeds are used most frequently. The 1.0 millicurie seeds are used almost exclusively in those larger tumors that are more cavernous in type.

Care has been taken to use small dosages. This has resulted in the necessity of making more than one application in several cases, but has avoided sloughing in any case, and in only one instance has there been a slight skin burn with resulting scarring.

FIG. 3.—Case 3: After treatment.

CASE REPORTS

Case 1.—W. G. A., white, male, age eight months, was admitted to Vanderbilt University Hospital, October 9, 1938. Patient had hemangioma of left lower eyelid since birth, with moderately rapid growth. On October 21, 1938, three radon seeds containing 0.25 millicurie each were implanted into the tumor. Results two years and three months later are shown.

Case 2.—R. N. C., white, female, age 12 years. Admitted, May 14, 1940, with large cavernous hemangioma of lip with capillary type hemangioma in the skin. On May 14, 1940, 15 radon seeds of 0.5 millicurie each were implanted. This did not cause total regression of the tumor. On July 15, 1940, ten radon seeds containing 1.0 millicurie each were implanted.

Photographs show patient at the age of 12, when first seen, and two years after second implantation.

Case 3.—M. L. H., white, female, age ten, was admitted, August 10, 1939, with tumor of left lower eyelid, slowing growing for several years. History of presence of tumor at birth could not be obtained. It was believed that the tumor followed trauma. On August 15, 1939, six radin seeds of 0.25 millicurie each were implanted.

Picture before implantation is not available but the lesion was comparable in size to that of patient in Case 1.

Pictures show results over one year later.

Case 4.—R. L. S., colored, male, was first seen December 21, 1938, with large capillary and cavernous hemangioma of cheek, present since birth. Due to delay in hospitalization and other illness, treatment was delayed for nearly a year.

A B

FIG. 4.—Case 4: A. Before treatment. B. After treatment.

On October 28, 1939, ten radon seeds of 0.5 millicurie were implanted. Complete radiation of the lesion was not attempted or expected at this time.

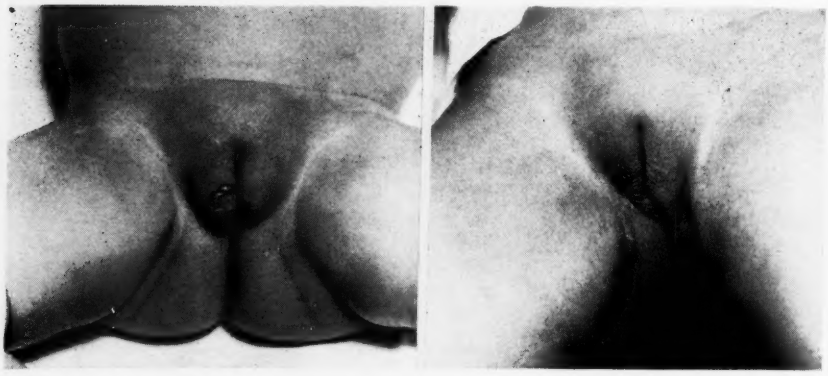
On December 4, 1939, 15 seeds of 0.5 millicurie each were implanted, on December 19, 1939, ten seeds of 1.5 millicurie were implanted.

Photographs show the condition before treatment, and 18 months after the first treatment.

Case 5.—R. E. B., white, male, age 15 months. First seen June 7, 1941. Hemangioma of lip first noticed at age of three weeks. It had grown rapidly. On July 28, 1941, five seeds of 0.5 millicurie each were implanted. This obliterated the capillary part of the tumor but failed to obliterate the more cavernous part of the tumor deeper in the lip. On November 6, 1941, four seeds of 0.5 millicurie each were implanted deep in the tumor. These were implanted through the mucous membrane to prevent scarring.

A B

FIG. 5.—Case 5: A. Before treatment. B. After treatment.



A B

FIG. 6.—Case 6: A. Before treatment. B. One year after treatment.

Pictures show condition before treatment, and two months following first treatment. Not enough time has elapsed to note the final results of treatment.

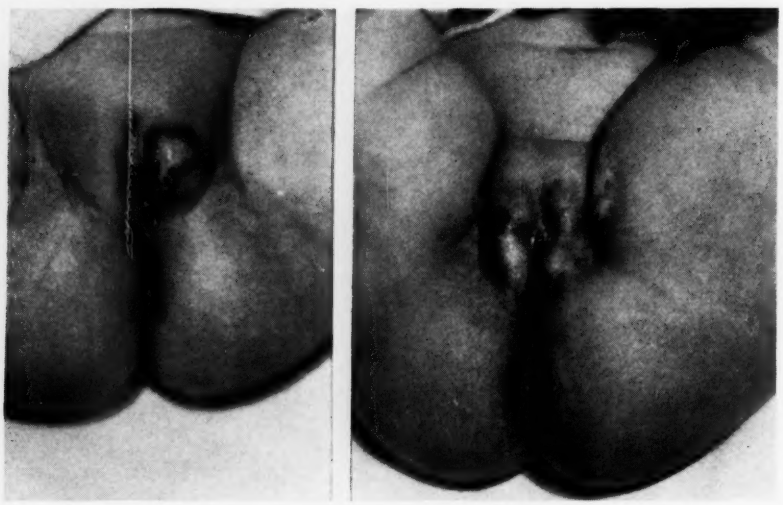
The next two case reports are rather unusual in that they do not occur in the region of the face but on the vulva. It was thought that excision of the hemangiomata and plastic repair would be difficult and unsatisfactory, and the same type of treatment was carried out as in those occurring on the face.

Case 6.—G. M., colored, female, age two years. Hemangioma of vulva present since birth, which gradually enlarged. On October 16, 1940, ten radon seeds of 0.5 millicurie each were implanted.

Photographs show condition before treatment and result one year after implantation.

Case 7.—J. K. B., white, female, age three months. Hemangioma of vulva, present at birth, began to grow rapidly during last month.

On August 27, 1940, 15 radon seeds of 1.0 millicurie each were implanted. This



A B

FIG. 7.—Case 7: A. Before treatment. B. After treatment.

dose was too large for this type of hemangioma. We were probably influenced by the rapidity of growth.

The patient suffered from swelling and desquamation of the vulva and has much more scarring than is necessary. There was no vulvar abscess.

Photographs show lesion before operation and approximately 15 months after operation.

SUMMARY

A brief discussion is presented as to the classification of hemangioma. The treatment of congenital hemangioma of the skin is briefly discussed, and cases treated by the implantation of radon seeds are reported.

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THE SURGICAL TREATMENT OF INTRINSIC KNEE JOINT LESIONS

FURTHER ANALYSIS OF OPERATIVE CASES

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THE PRESENT DISCUSSION of this important subject is based upon experience accumulated through years of more or less constant contact with the problem. In previous communications a total of 186 operative cases were reported.[1, 2, 3] The experience from January, 1932 to July, 1941, consisting of 189 arthrotomies, forms the basis of this communication, making a total of 375 cases cared for with basically the same operative criteria and technic as outlined by the senior author (J. J. M.), in 1932. Slight modifications have been adopted as needed but the general schema has been preserved intact. We believe that emphasis is to be placed on proper diagnosis and the understanding of definite indications for operation rather than on the actual operative technic. The surgeon must decide which cases are surgical and which require medical care alone. Of those which come into his field, he must decide which are to be operated upon and which are to be treated conservatively. Not only the presence of abnormalities but their degree of severity must be estimated in making an operative decision. A knee operated upon is never again a wholly normal joint, and hence the candid surgeon refuses to replace minor pathology by man-made defects causing equal or greater disability.

PATHOLOGIC ANATOMY

It must always be remembered, especially by the occasional operator, that the presence of multiple abnormalities is the rule rather than the exception.

Semilunar Cartilages.—The semilunar cartilages are not stationary. They move forward when the knee joint is extended and backward when it is flexed. A moment's reflection shows why this is necessary. The phenomenon is easily demonstrated on the fresh cadaver or at the operating table. The internal cartilage is approximately semicircular. It is the larger of the two and is firmly attached at its medial margin to the medial (tibial) collateral ligament. The external cartilage is smaller, nearly circular in outline and its attachment to the lateral (fibular) collateral ligament is narrower and less substantial. This is also easily demonstrable and accounts, in part at least, for the great preponderance of internal meniscus derangements. The cartilages are subject to various abnormal conditions:

1. Fracture-dislocation—the most frequent injury.
2. Dislocation without fracture.

3. Fracture without dislocation.
4. Erosions—irregularities of the cartilage surface usually encountered in the later stages of knee joint osteo-arthritis.
5. Cysts: These are of obscure origin. They usually contain a grey-yellow viscid fluid. Some are thought to be due to injury followed by mucoid degeneration, others possibly to synovial developmental inclusions.[4] Because of their rarity they are of minor importance.
6. Developmental anomalies: These include the "discoid" cartilage which is said to be a persistence of the embryonic disk-shaped form. We have had no experience with this condition.

Synovial Membrane.—The synovium of the knee joint is the largest in the body. Because it must accommodate itself to a great variety and range of motions, it is normally loosely folded on itself. Of the entire joint structure it alone contains sensory nerve endings and hence subjective pain is expressed in terms of synovial irritation. All internal derangements are accompanied by a varying degree of synovial hyperemia and extravasation of fluid. If the irritating body is not removed this membrane becomes permanently thickened and irregular. Calcium deposits appear, and, becoming detached, give rise to multiple, small loose bodies. The late result of a chronic traumatic synovial irritation is the so-called hypertrophic or villous synovitis. Synovial adhesive bands often appear following irritation or hemorrhage. The *subpatellar fat-pads* partake of this general synovial swelling. Frequently they enlarge to such a degree as to intrude themselves between the joint surfaces when the knee is extended. At operation, the tips show a characteristic reddened "pinched" appearance and they also may eventually become calcified and detached, giving origin to a loose body.

The *joint surfaces* of the knee undergo progressive changes, which may be thought of as due to wear and tear. This degeneration is hastened by overweight, by overuse, or by the continued presence of loose bodies or other joint irritants. In general, the changes are indistinguishable from an *hypertrophic osteo-arthritis*, characterized by irregular bony overgrowth and marginal osteophyte formation. *Osteochondritis dissecans* is an obscure condition in which a fragment or fragments of cartilage and underlying bone are detached from a joint surface. In the knee the source is usually the mesial articular margin of the internal femoral condyle. The detached fragments then become loose bodies and their continued presence cause the usual secondary changes. It is said that the medial condyle of the femur can be injured by the medial meniscus when sudden backward pressure is brought on the hyperextended knee.[5] This is a separate entity and probably should not be confused with osteochondritis dissecans.

Calculi of indeterminate origin are frequently found. They are different from the joint mice of osteochondritis dissecans because they are smooth and convex on both sides while the latter usually have a rough, concave side corresponding to a defect on the femur. Locking may be the first symptom of their presence.

Diagnosis.—By far the most important single aid in achieving the proper understanding of any particular case is the *history*. This should include a minute and exact catechism on the mode of injury and subsequent course. One should convince oneself as to the *adequacy* of the alleged trauma. It is also important to accurately understand descriptive terms as applied by the layman. For example the term "locking" is often used to describe *difficult* extension of the knee due to pain, whereas, actually, it should mean an insurmountable wedging of the joint. This is a very important distinction.

Mode of injury is often difficult to determine and may be buried in the dim past. In our series of cases, the average interval between the first connectable injury and operation is somewhat less than 27 months. The earliest case was operated upon one week after trauma, while the longest elapsed time was 50 years. Ferguson and Thompson,[6] reporting 100 cases, state that the average time from injury to operation was two and one-quarter years, which nearly exactly corresponds to the time-interval in the present series. The most common type of violence is a "twisting" or "wrenching," with the affected knee in a partially flexed position (42 per cent of our cases). Direct violence to the knee without twisting or wrenching was mentioned in 16 per cent of our cases, and an equal number gave a history of a "fall," without definite recollection as to the mode of injury. Fifteen per cent gave no history of trauma whatsoever and, of these, spontaneous locking was the presenting symptom in two cases. A small group (seven per cent) gave a history of locking of the joint on arising after prolonged kneeling, stooping or sitting. Another small group consisted of cases of severe injury about the knee (2 fractured femora, 1 fracture of patella, 1 dislocation of knee) in which the cartilage injury became apparent only after the major damage had been repaired. One case had been injured by a bullet, and another by a retained foreign body.

TABLE I

MODE OF INJURY

	Per Cent
Twisting or wrenching violence	42
Direct violence, without knowledge of fall or twisting	16
Fall, without definite knowledge of mode of injury	16
No history of trauma	15
Locking of knee following prolonged stooping or kneeling	7
Internal derangement masked by major fracture or dislocation	3
Foreign body and bullet wound (one case each)	1
Total	100

Following the original injury a varying amount of swelling, pain, and stiffness supervenes. It usually regresses in two or more weeks, and the patient may have only minor difficulty for a long time, characterized by a vague feeling that the knee "is weak" or that it "doesn't feel right." The history often becomes one of repeated minor mishaps followed by pain, limitation of motion, or knee joint effusion. Locking may appear early or late. It is a capricious but important symptom. Frequently the patient complains of "clicking" or "grating" sensations, especially on forceful extension of the

joint, as on climbing stairs or arising from a chair. Weakness and "giving way" of the knee become especially frequent on going downstairs. The location and character of pain is carefully noted. Occasionally a loose body in the joint will be felt by the patient and demonstrated at different points in its peregrinations around the knee. Loss or gain in weight is always of importance in evaluating the capabilities of a knee joint. Finally, it is of utmost importance to inquire into the bleeding tendencies of a prospective operative patient and, if necessary, to determine the bleeding and clotting time.

Physical Examination.—Adequate exposure is insisted upon. One observes particularly the gait and the presence or absence of muscle atrophy, especially of the quadriceps group. A markedly atrophic thigh makes a poor operative risk, and insures a slow, unsatisfactory postoperative course. Comparative measurements of girth at certain levels can be made and recorded for future reference. Limitation of active and passive motions is determined—always bearing in mind the rôle of pain and voluntary muscle spasm.

When swelling is present, one should determine whether it is due to fluid or to synovial thickening, or both. The rim of the tibial plateau is explored carefully with the knee in both flexion and extension. In this way, telltale tenderness or small irregularities are discovered.

Crepitation is often best observed with the palm of the hand on the patella while the joint is opened and closed. Variations can be estimated audibly by means of the stethoscope, and, with the practice attained by making such an examination a routine, information of value is obtained.

Roentgenologic examination is a routine in all operative cases and in those in which there is a history of trauma. As in a great many other locations, the positive film is of considerable value but an entirely negative film is of somewhat lesser importance. Operative decisions, in general, are made from clinical criteria. The knee is taken in three views—(1) anteroposterior; (2) lateral; and (3) postero-anterior. The technic and posturing are shown in the accompanying diagrams (Figs. 1, 2 and 3). A fourth view is very occasionally used (Fig. 4). Obviously, the marked degree of flexion necessary will be impossible to obtain in most cases. It silhouettes the femoral articular surfaces and the under surface of the patella. In the three routine views note that the central ray beam is always parallel to, and just above the tibial plateau.

GENERAL CONSIDERATIONS

This series of 189 knee joint arthrotomies was performed upon 170 patients. Fifteen patients were operated upon twice, and one patient no less than five times (for rapidly recurring pain and disability due to osteo-arthritic spurs and hyptertrophic synovitis, with calcification and multiple foreign body formation). There were 137 males and 33 females. The average age was 33.7 years (males, 32.8; females, 37.3 years). The oldest was 67 and the youngest 13. One hundred forty-seven arthrotomies were performed

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FIG. 1.

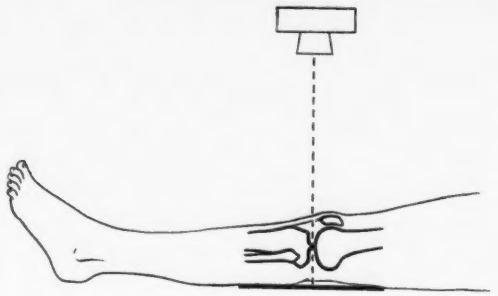
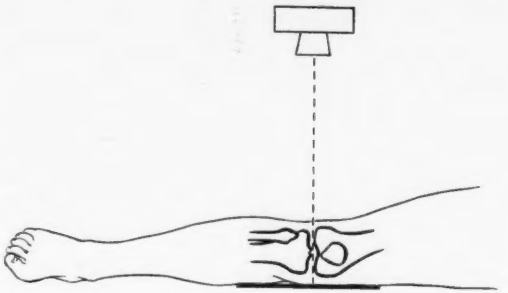


FIG. 2.



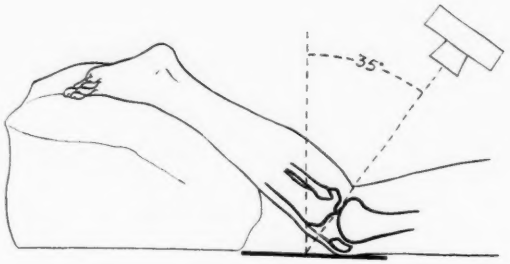


FIG. 3.

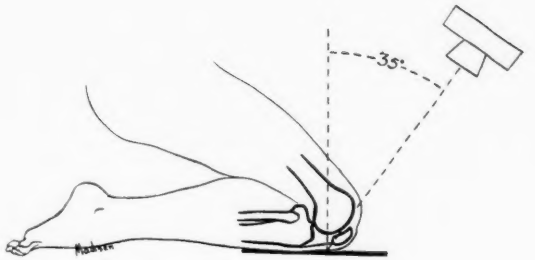


FIG. 4.

FIG. 1.—Routine anteroposterior view.

FIG. 2.—Routine lateral view. The knee is flexed about 30°.

FIG. 3.—Routine postero-anterior view. Foot supported by pillow. This opens intercondyloid notch.

FIG. 4.—Optional view. Limited use. Sometimes of value in demonstrating abnormalities missed in routine roentgenograms.

upon males; 42 upon females. In the males the great bulk of patients were between the ages of 20 and 35 and, on the whole, were an active, healthy well-developed group consisting chiefly of workmen and exathletes. One hundred three (70 per cent) of the males had frank cartilage derangement. Ten (seven per cent), presented severe meniscus erosion, necessitating removal. Eight (five per cent) showed typical osteochondritis dissecans, with loose body formation, and six (four per cent) contained loosed bodies (calculi) of doubtful origin. The remaining group of 15 (14 per cent) consisted mostly of hypertrophic oseo-arthritis, with a sprinkling of rarer conditions. A survey of the females operated upon showed that less than one-half presented cartilage injuries. These appeared mostly in younger women and girls injured in sports. As the average age of the females was higher than that of the males, one would expect a larger percentage of hypertrophic osteoarthritis. Such was the case.

The *differential diagnosis* of surgical lesions of the knee joint is best made if the above factors are kept in mind while making the routine examination.

Derangement of the Cartilages.—This is the most common erroneous diagnosis. A typical history of injury with locking followed by joint effusion and joint tenderness *directly over* the internal meniscus is not always obtained. In our experience, definite locking was present in about one-half of the cases of proven cartilage derangement. It is not a necessary symptom. The exact figure is hard to arrive at. So-called "bucket-handle" fracture (detached except at either end) was the most consistent cause of locking (75 per cent of the time). Other proven cases of cartilage derangement, plus loose bodies in the form of calculi and the remnants of osteochondritis dissecans, caused locking in only one-half the cases. It is interesting to note four cases of locking in which no loose bodies of any kind were found. These may have been occasioned by temporary abnormal mobility of the cartilages.

In acute cases *roentgenograms* usually show only capsular distension, with a floating patella. Narrowing of the joint space on the side of the deranged cartilage, as seen in the anteroposterior exposure has not been a common finding in our experience. Sprain of the internal collateral ligament of the knee is to be differentiated by location of maximum pain and tenderness about one inch above the cartilage level over the medial condyle of the femur. The external meniscus derangement (only four cases in this series) is diagnosed with difficulty. Tenderness over this cartilage is usually misleading.

Knee joint calculi and loose bodies associated with osteochondritis dissecans often appear without alleged trauma (although some knee injury usually can be recalled by anyone, if sufficiently interrogated). The migrating offender may be felt in the quadriceps pouch or may appear and disappear at various locations on the periphery of the joint. Roentgenograms visualize these types of loose bodies if they contain sufficient calcium or if not ob-

scured by superimposition of dense bony shadows. In the case of osteochondritis dissecans careful roentgenologic study, in various oblique views, may reveal an irregularity of bony contour in the region of the lateral aspect of the medial condyle of the femur.

Hypertrophic synovitis and hypertrophy of the subpatellar fat-pads are to be expected as sequelae to long-standing intrinsic knee pathology, particularly those conditions causing repeated traumatic synovitis with bloody or serous extravasation. Enlarged fat-pads may interpose between the femur and tibia when the knee is brought to extension. In such a case, continued extension meets relative, not absolute resistance, and is painful but not impossible. This is not *true* locking.

Hypertrophic osteo-arthritis is evidence of wear and tear on the knee joint. Typical joint changes, with spur formation, occur, due to untreated joint calculi after many years' trouble and are monarticular. *Both* knees are involved as part of a generalized osteo-arthritis, which manifests itself in one or both joints due to increase in weight, postural defects, or other situations which result in abnormal or overuse. An advanced degree of arthritis may be present for years and never manifest itself until one of these precipitants occurs. These joints develop considerable limitations of motion, with or without severe pain. At times, crepitations due to destruction of cartilaginous bearing surfaces becomes so loud as to be heard across the room.

TREATMENT

Nonoperative.—This is often the lesser of two evils, and is carried out by the conscientious surgeon in the face of many importunings to be more radical. Emergency arthrotomy is never employed except in the presence of irreducible locking. Points to be emphasized in a conservative therapeutic regimen are:

1. *Weight reduction* undertaken slowly and carefully, with proper attention to vitamin intake and avoidance of debility.

2. *Posture.*—This includes special instruction in proper walking and particularly to correct pronated, weak feet. The patient should attempt to toe-in, and bear the weight on the outside of the foot. A lift (one-quarter-inch) on the inside of heel and sole often helps to readjust the weight-bearing axis. Foot exercises for muscular strengthening are of value.

3. *Exercises.*—It must be remembered that of all of the muscles of the body the quadriceps femoris atrophies the quickest. Hence, the emphasis is on early, active repetitive motions to maintain this important muscle. No knee is stable or safe from future debacles if activated by a weak or flabby quadriceps. "No knee is stronger than its quadriceps."

4. *Aspiration.*—This is carried out with careful attention to sterility. In fresh injuries a sanguineous or serosanguineous fluid is aspirated, whereas later the fluid is found to be straw-colored and more viscid. Following aspiration the joint is firmly bound with a three-inch bandage of the ACE-

type. Remarkable relief of pain sometimes occurs when a tense capsule is decompressed.

5. *Physiotherapy.*—Baking and massage are of considerable aid in relieving the swollen, painful joint. The indescriminate use of short-wave diathermy, and allied modalities, is to be condemned. These impressive machines tend to take the place of thought on the part of the surgeon and effort on the part of the patient. Certainly, it is unwise to attribute to them any specific virtue.

Operative Intervention.—This is chosen only after a reasonable amount of conservative treatment has been unavailing. Operation is undertaken for persistent or recurring disability due to internal derangements and for recurrent locking. In these cases one must not wait too long before operating because irreversible changes take place. Such secondary developments as hypertrophic synovitis, osteo-arthritis, or enlarged subpatellar fat-pads are only partially remediable. One occasionally operates with the specific idea of prophylaxis but, of course, only when the diagnosis is definite.

Unfortunately, many patients refuse surgical intervention, preferring to temporize with minor, but ever increasing disability. They are to be seen painfully limping, often with flexion contractures and in the end stages of joint destruction. But even here, if the musculature is capable of preoperative activation and with complete cooperation on the patient's part, one can hold out, tentatively, some relief from an operative "cleaning out." Likewise, selected cases of recalcitrant hypertrophic osteo-arthritis, unassociated with trauma, can be operated upon, but, again, the potential rehabilitation must be envisaged. The question of excision of the patella will be briefly taken up below.

Preoperative Preparation.—The patient is admitted the afternoon of the day before operation. The entire thigh, leg and foot is shaved, washed thoroughly with green soap followed by alcohol and then ether. It is carefully wrapped in sterile dressings which are kept wet with a solution consisting of four cubic centimeters of tincture of iodine to 500 cc. of saline. Bleeding and clotting times are determined where indicated—this could probably be made a routine, with profit. A light cathartic is administered in the early evening and followed, if necessary, by a low saline enema the next morning.

Choice of Anesthesia.—Morphine and scopolamine are administered one hour preoperatively as a routine. The usual case is handled readily by a low spinal anesthesia, since about one hour is the elapsed time from the application of the tourniquet until its removal. Avertin-gas-oxygen-ether sequences or cyclopropane are frequently employed when the patient is of an apprehensive type.

Operative Technic.—This has been described at length elsewhere.[1, 2] An Esmarch bandage is wound tightly while the leg is elevated, to render it bloodless, and the tourniquet applied to the upper thigh, making sure that the femoral vessels are well padded. The tourniquet should not be used

in the presence of advanced arteriosclerosis or peripheral vascular disease. None of our cases were denied its use. The patient lies supine on the table. Draping of the extremity is carried out so that complete mobility is possible without restriction. Rigid Lane-technic is adhered to throughout. This includes additional precautions in the preparation of the operative field, a general "hands off" policy, and the sterilization of each instrument after each operative step. Suture material is handled only with instruments. No vessels are ligated.

Type of Incision.—Many ingenious approaches to the knee joint have been devised. All have certain disadvantages. The split-patella approach gives excellent exposure but seems unnecessarily mutilating. Besides, it requires a postoperative plaster of paris casing. Moder[9] make a U-shaped central skin incision and turns the skin flap upwards. The patella tendon is split vertically and the patella dissected out. This also would give excellent exposure but we believe routine excision of the patella to be unnecessary. The incision used by Haggart and Toumey[8] involves the turning of a medial skin flap. Following this, the joint is exposed *via* two vertical incisions—before and behind the internal lateral ligament. It permits removal of the entire medial meniscus but wide exploration would not appear to be possible. We continue to employ the mediolateral incision because it permits wide exploration and early, active mobilization. We believe that in the rare, early case a short (three-to-four-inch) incision can be made, always with readiness to enlarge it. In all recurrent or late cases the incision is made long enough, usually five to seven inches, to permit dislocation laterally of the patella. This permits wide exploration, visualizing both menisci, the character and contents of the quadriceps pouch, and the under surface of the patella. Surgical attention to enlarged fat-pads, synovial and bony excrescences is readily given. As in abdominal surgery, one operates with a definite diagnosis in mind but continues the analogy to the knee in maintaining that exploration is part of the "celiotomy" of the knee joint.

ANALYSIS OF CASES

Of 189 cases operated upon the internal meniscus was removed in 139 (74 per cent). In addition, three cases, previously operated upon elsewhere, showed sizeable remnants amounting to perhaps half of the cartilage. These were removed with relief of symptoms. Of the 139 cases subjected to removal of the internal cartilage, 121 showed evidence of fracture or dislocation, or both. About one-third of these (36 per cent) showed the "bucket-handle" deformity. Seventeen cartilages were removed because of marked "erosions"—irregularities associated with other changes in the joint. One cartilage was removed because of cyst formation.

The external cartilage was removed a total of eight times—four times for frank injury, and four times for "erosions."

Hypertrophy of the subpatellar fat-pads was of sufficient degree to require removal of 64 cases. Partial synovectomy was carried out in 61 cases. Loose

bodies of all types were removed in 26 cases, varying in size from the tiny "rice-bodies" to almond-sized or larger calculi. Bony spurs and irregularities were removed in 21 cases. In seven cases bony defects corresponding to the location of an osteochondritis dissecans were found and smoothed off. To those who advocate the buttonhole exposure of the knee joint the following is of interest: Of the 121 cases of frank cartilage injury, other abnormalities (of the synovium, fat-pads or bony structures) of sufficient degree to warrant surgical attention were found in 77 (64 per cent). Most of these defects would not have been seen, let alone remedied *via* the small incision. The sole objection to the long incision is the length of the scar. However, in our experience, healing occurs with rapidity and safety.

In three cases of far advanced hypertrophic osteo-arthritis the patella was removed. In two of these the patella had become fixed to the femoral condyles causing marked limitation of motion. The other case presented extreme destruction of articular cartilage. Motion was painful, slow, and accompanied by a hair-raising "screak" audible across the room. At operation, it was found that deep grooves had been gouged on the femoral surface by the offending patella. In another case of far-advanced hypertrophic osteo-arthritis, arthrodesis was performed for relief of pain.

There was one cystic protrusion into the joint, apparently arising from the synovium over the external lateral ligament. In another case, a similar excrescence was found growing from the anterior cruciate ligament near the attachment of the medial meniscus. One arthrotomy was performed to remove a darning needle which had worked its way into the joint.

Postoperative Treatment.—A large "muff"-dressing, consisting of several layers of sterile absorbent cotton, is firmly applied from midthigh to mid-calf before the tourniquet is released. Snugness is obtained by bandaging over the cotton with several layers of five-inch muslin. The patient is put to bed with the extremity elevated on one or two pillows. The following day a cradle is installed to support the bed clothes and to facilitate exercises. For warmth a 60-watt bulb is kept under the clothes, although this may not be necessary in summer time.

At the earliest possible moment exercises are begun—usually from 36 to 72 hours postoperative. The first maneuver is for the patient to reeducate the quadriceps by "shrugging" the patella. It may take a day or two for some patients to regain the ability to contract the quadriceps while others begin immediately. Often, in face of pleas of pain, a forceful demeanor is necessary to secure cooperation on the part of the patient. The next step requires him to lift the extended leg off the bed. This can usually be done in three to seven, occasionally more, days. The patient is allowed in a wheel chair on the 4th or 5th day. Sutures are removed on the 7th to 10th days, and the patient encouraged to walk. He pushes a chair ahead of him at first and, when able, graduates to a cane. Crutches are not used.

Systematic, repetitive exercises, designed to use the quadriceps muscle and bend the knee, are performed daily, until atrophy is no longer present. Swim-

ming is an excellent exercise of this type, particularly the so-called "crawl" kick. After the leg can be raised with ease the opposite or "good" leg is laid across it and its weight added to that of its mate. Later, forceful resistance can be applied. For office workers and people at home, placing a waste basket over the foot, with or without weights, increases the effort necessary for extension.

Postoperative *aspiration*, routinely proposed by some,[7] we use exceedingly rarely. Physiotherapy is employed in the form of baking and massage daily or three times a week until adequate motions are restored. The whirlpool bath is of great help in selected cases. However, it must be emphasized that nothing takes the place of conscientious muscular effort on the part of the patient. The office worker returns to work in four to six weeks. The laborer may require six to eight weeks, and in some of the more perilous callings even more.

Postoperative Complications.—There was one case of gross joint *infection*, eventually necessitating a midthigh amputation. During an acute postoperative mania this patient tore off his dressing and had to be transferred to a psychiatric hospital. A second case was discharged with apparent primary union. One month postoperatively, redness and heat in the wound led to abscess formation, necessitating drainage. The joint space was not involved nor was the final result compromised in any way. No other infections occurred. *Hemorrhage:* In one case, wound healing was delayed by hemorrhage with clot formation. The wound was reopened down to the synovium, cleaned and resutured. Excellent healing was obtained. There were no deaths, nor were there any severe pulmonary complications in this series.

Results.—Uniformly good results are anticipated in cases of cartilage derangement, loose body formation or other nondegenerative situations where the patient is young or in early middle age and secondary changes of an irreversible nature have not yet supervened. The importance of pre- and postoperative quadriceps activation is to be emphasized.

In the series operated upon for relief of pain and disability due to advanced osteo-arthritic changes, with or without hypertrophic or calcific synovial changes, only about one-half achieve permanent improvement of substantial degree. The rest generally show improvement for six to twelve months, when progressive changes again evidence themselves. Patients will sometimes beg to be operated upon again, as in the one case in which revision was undertaken four times on the left and once on the right side in a period of four years. Each time symptoms returned after about six months relief. In this regard the subject of excision of the patella comes up. The status of this procedure has not yet been established and, certainly, our three cases are not enough to allow any conclusions to be drawn. We note, however, that the deformity due to change in contour is almost unnoticeable. It has been said that one of the functions of the patella—since it lies mostly beneath the patellar tendon—is to keep the pressure of the tendon from impinging

on the synovial membrane overlying the anterior femur. It is reasoned that a slightly inflamed synovium will cause painful motion if the suspensory action of the patella is removed. We have had no definite indication that this is the case. Of the three cases, one obtained an excellent painless knee. In one, motion and function were restored, but after six months pain and disability recurred. The third case obtained freedom from pain and greatly increased motion but shows marked weakness in extension, due apparently to separation of some of the central fibers of the patellar tendon.

SUMMARY

1. One hundred eighty-nine knee joint arthrotomies are added to previous reports, making a total of 375 cases.

2. Nonoperative methods and criteria for operations are discussed.

3. Operative routine used includes: (a) Meticulous preparation; (b) use of tourniquet; (c) careful Lane-technic; (d) use of mediolateral curved incision of length adequate for exploration; and (e) tight "muff"-dressing.

4. Postoperative routine emphasizes early active motions.

5. Complications consisted of: (a) Two infections—one following an acute mania, during which the patient tore off his dressing; the other occurring one month postoperative, after apparent uneventful healing; and (b) hemorrhage in one case, necessitating resuture of the wound, without impairing the final result.

6. End-results, and their anticipation, are discussed.

7. Removal of the patella in cases of advanced osteo-arthritic changes is briefly considered.

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A LIGHT, COMPACT UNIT FOR THE INTRAVENOUS OR INTRAOSSEOUS INJECTION OF PLASMA IN EMERGENCIES

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THE PRESENT FORMS of apparatus for administering plasma are heavy, expensive, bulky to transport, complicated to set up, require a standard or upright, and the overall time of administration is long. Figure 1 compares the weight and size of the units now in use with our compact container.

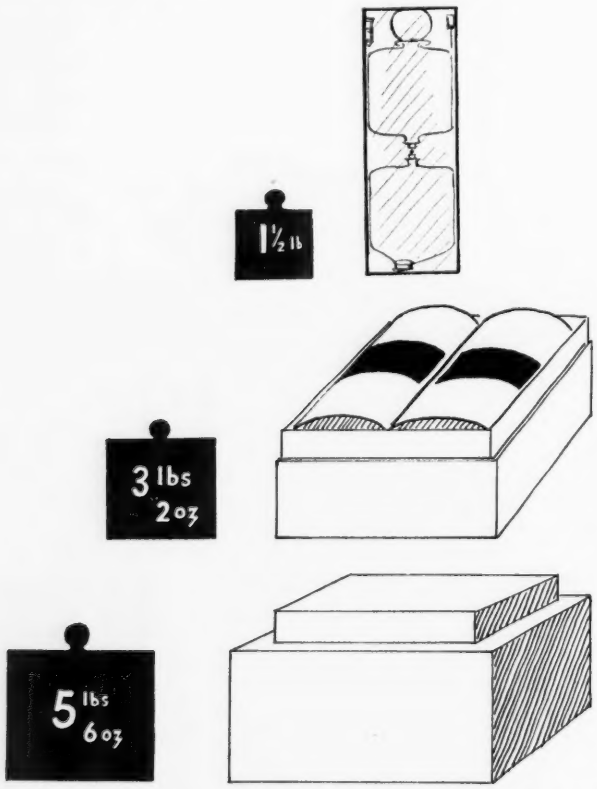


FIG. 1.—Comparison of the weight and size of described unit (1) with two other units now available (2) and (3), all containing approximately the same amount of dried plasma.

Under conditions of warfare, with the ever present menace of casualties among combatants and the civilian population, there is need for a small, compact, lightweight, durable, refillable unit by which plasma can be administered rapidly under adverse and ideal conditions.

Previously described units[1, 2] are not designed for the emergency admin-

istration of plasma to those patients whose circulatory depression is so marked that it is difficult or impossible to introduce anything into their circulation by the venous route. It is at this time that fluids are most urgently needed and the intra-osseous route should be used.[3] With the simplified apparatus here presented, for injecting plasma rapidly into the acutely disabled patient, it is possible to administer 16 to 20 grams of plasma (dry weight) intravenously or intra-osseously within five minutes after beginning operation. The average time is four minutes.

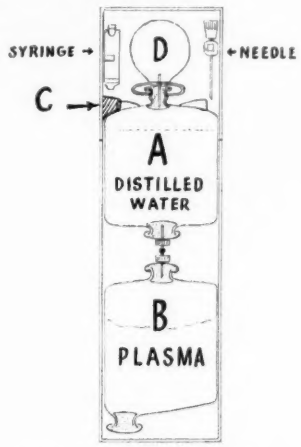


FIG. 2.—Arrangement of the unit: A. Distilled water bottle. B. Plasma bottle. C. Retaining flange. D. Rubber pressure bulb.

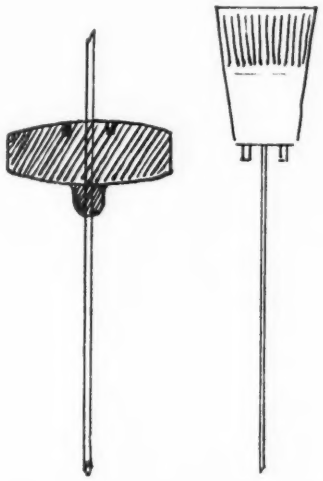


FIG. 3.—Dual-purpose needle with the stylet removed.

The unit (Fig. 2) filled and packed for transit weighs 680 Gm. (1½ pounds). The complete apparatus measures 22.5 cm. (8¾ inches) long x 6 cm. (2 5/16 inches) in diameter, and can be packed in a metal can under vacuum. The diameter of the container is comparable with the average water glass and is easily held in the hand. The dual-purpose needle and the syringe are mounted in the upper cover. In use, no part of the apparatus need be laid aside; it can be operated without any accessory equipment or aid. The entire amount of fluid may be given without danger of administering air, as the lower end of the bottle is tapered and the transparent cylinder makes the plasma level visible during the entire administration.

The unit (Fig. 2) is composed of two 120 cc. pyrex glass bottles, with openings at both ends. Mobile Bottle A, containing 100 cc. of sterile pyrogen-free water with 0.1 per cent sodium chloride, rides in key-way when top cover is removed. The flange (C) in the upper cover holds the winged-arms of the upper bottle and prevents rotation and motion during transit or handling. Fixed Bottle B contains 16.5 grams of desiccated human plasma representing 250 cc. of original liquid pooled plasma. This dried plasma is packed under vacuum of 73.6 cm. (29 inches) Hg. The bottles are mounted in a metal, fiber, or transparent plastic case which holds them securely. The

FIG. 4.

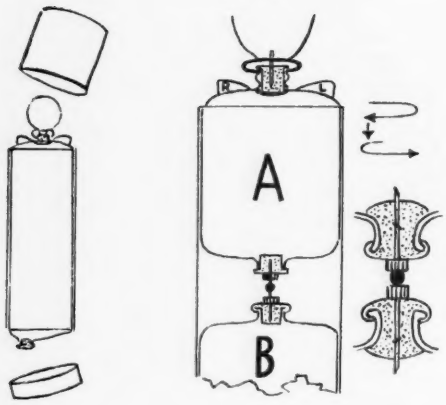
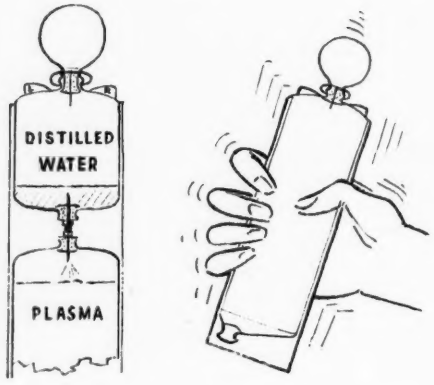
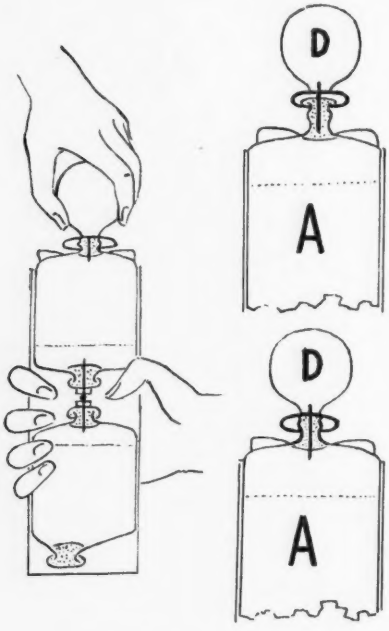


FIG. 6.





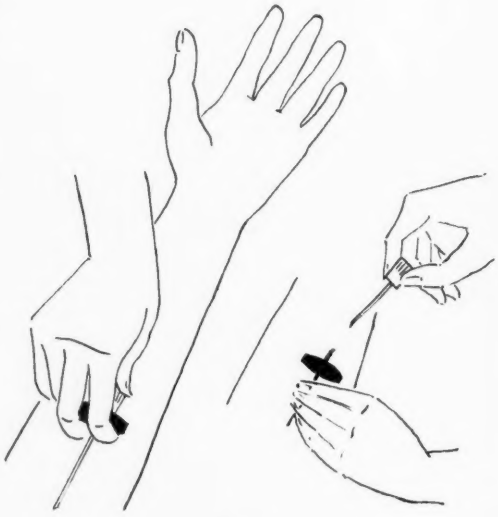


FIG. 5.

FIG. 7.

FIGS. 4-7.—Steps in the technic of administration of plasma intravenously. *(Remaining steps illustrated on page opposite.)*

clearance between the pyrex bottles and the plastic covering is 1/64 of an inch; this prevents damage to the contained bottles if dropped or jarred. All four openings are covered with hood-type neoprene or rubber stoppers. A double-pointed needle of gauge No. 18 is suspended between the two bottles so that the downward movement of the water bottle A results in puncture of the central stoppers of the water bottle and the plasma bottle. When ready to restore the plasma to the liquid state the rubber bulb D (with cotton filter) is pushed home, the metal clip catching over the flange of the water bottle. The vacuum in the plasma bottle causes the distilled water to flow from

bottle A into bottle B. If, for any reason, all the distilled water fails to go into the lower bottle, it can be forced in by compressing rubber bulb D. The entire unit is then shaken until the plasma is completely in solution.

The dual-purpose No. 16-gauge needle (Fig. 3) is made of stainless metal and has the 3 mm. bevel parallel to the winged-arms, thus, facilitating intravenous insertion. The winged-arms and the tapered stylet-head allow better purchase, aid in the intra-osseous insertion, and facilitate the removal

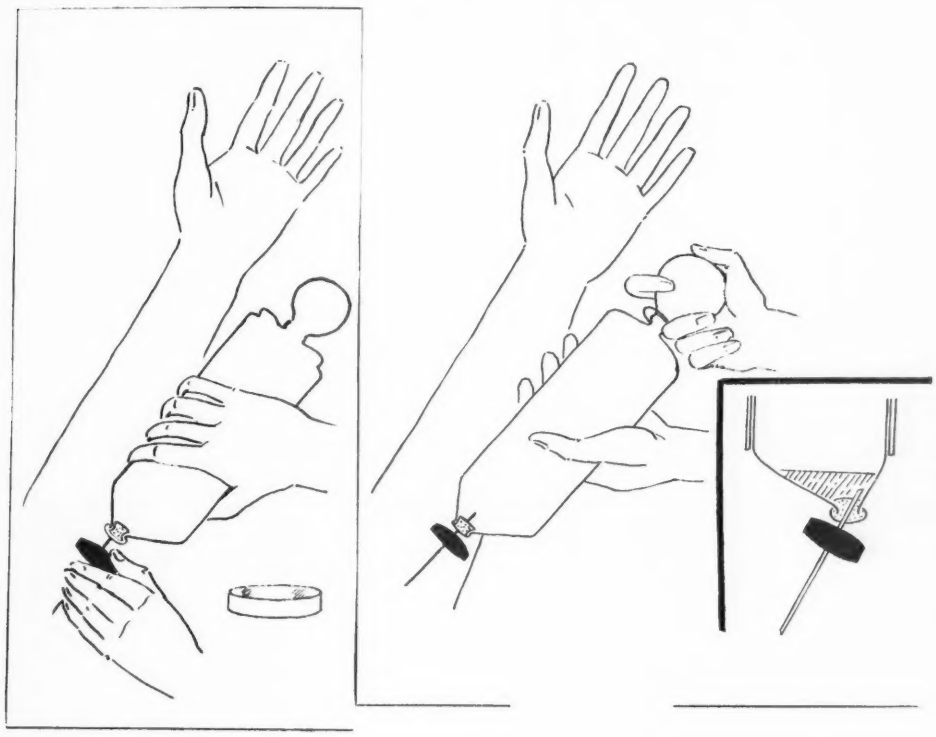


FIG. 8. FIG. 9. FIG. 10.

FIGS. 8-10.—Remaining steps in the technic of administration of plasma intravenously

of the stylet when the hands of the operator are wet, oily, or bloody. The needle does not clamp on the glass lip extending from bottle B but rides in the rubber stopper allowing some free play, thus, preventing breakage of the glass tip that would occur from motion of the operator's hand transmitted to the rigid needle fixed in the bone.

PROCEDURE FOR INTRAVENOUS ADMINISTRATION OF PLASMA

(1) The large end section of the container is removed and the winged-arms of the protruding bottle are turned clockwise, pushed into the cylinder, then rotated counter clockwise to lock bottle A in place (Fig. 4).

(2) The container is held upright. The rubber bulb D is now pushed home, the metal clip catching over the flange of the upper bottle (Fig. 5).

(3) When all the water has entered bottle B, the container is then agitated for one minute (no less) in order to restore the plasma to a fluid state (Fig. 6).

(4) Remove sterile needle from the top container; insert the needle into vein and then remove the stylet (Fig. 7).

(5) Remove lower cover of container. The rubber stopper of bottle B is now punctured by that portion of the needle extending proximal to the winged arms (Fig. 8).

(6) With the patient lying down, the arm is elevated distally so the container is as near upright as possible, and then by intermittent compression of bulb D the plasma is forced into the vein (Fig. 9).

(7) When the fluid level reaches the red line on the lower bottle, stop compression of the bulb and remove the needle (Fig. 10).

FIG. 1

PROCEDURE FOR INTRA-OSSEOUS ADMINISTRATION OF PLASMA

The first three steps are the same as described above.

(4) Remove sterile needle with stylet in place from the container and insert it into the bone (Fig. 11a).

FIG. 1

TECHNIC FOR INTRODUCING NEEDLE IN THE MARROW

The site of choice for the injection in patients over five years of age is the manubrium, one centimeter above the angle of Louis, or the body of the sternum, at the third interspace, in the midline. After preliminary local anesthesia with procaine (when possible or necessary), the needle, with its stylet, is inserted vertically with the bevel towards the head of the patient. The periosteum is penetrated gently with a semicircular burrowing motion until a firm hold is obtained. The needle is then tilted, its tip pointed toward the neck of the patient and with the same burrowing motion, the anterior plate of the sternum is penetrated. The needle should not be "jabbed in" or pushed in with force. When the marrow cavity is penetrated, diminution in the resistance to the progress of the needle is felt, amounting sometimes to a trapdoor effect. In the hands of the inexperienced, there is less danger of injury if the needle is inserted in the upper end of the tibia, than in the sternum.

FIG. 1

(5) Once the needle is properly fixed in the bone the stylet is removed (Fig. 11b).

(6) The small syringe is then attached and a few drops of bone marrow aspirated, to make sure that the needle is properly placed in the marrow cavity. The syringe is then removed (Fig. 11c).

(7) The rubber stopper of the lower end of bottle B is punctured by that portion of the needle extending proximal to the winged arms (Fig. 12).

(8) By intermittent compression of bulb D, the pressure in the closed system is increased and the plasma is forced through the needle into the marrow and, ultimately into the circulation of the recipient (Fig. 13a).

(9) When the fluid level reaches the red mark on the lower bottle, the

unit is removed (Fig. 13b). The needle is then withdrawn with the same type of semicircular twisting motion used in driving it in.

This plasma injection unit has been tried 20 times in 20 patients, with satisfactory results.

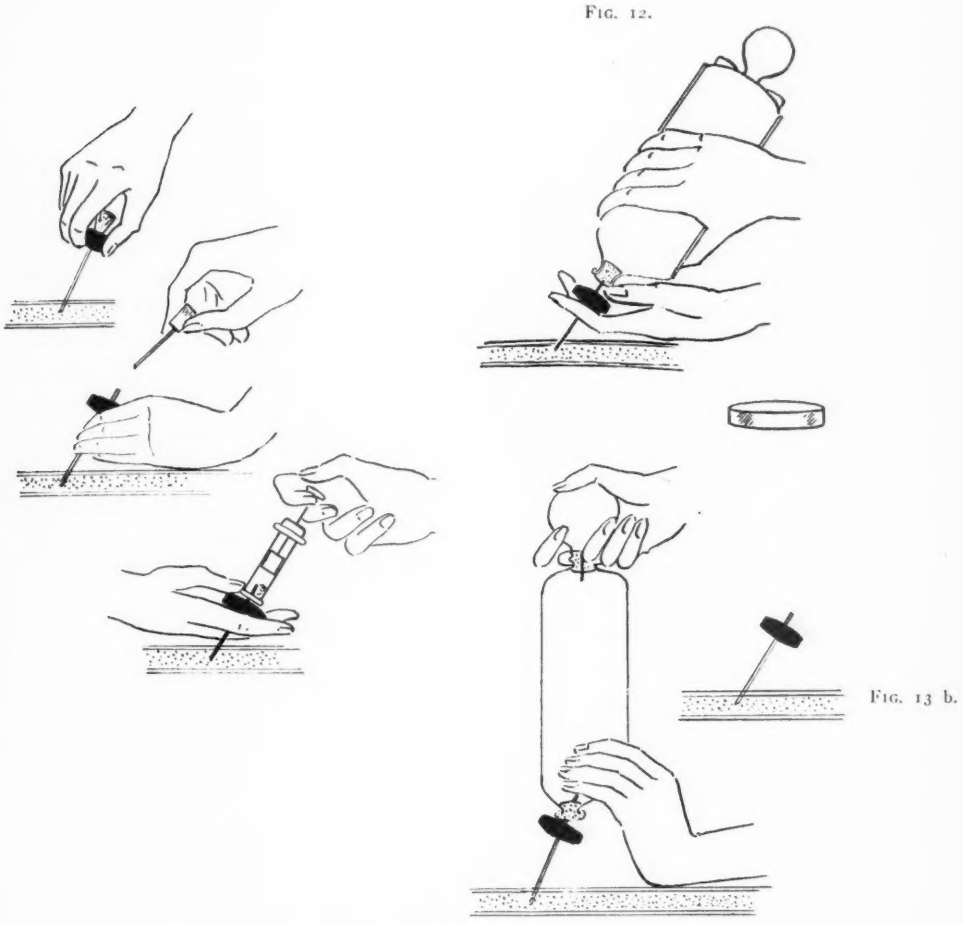


Fig. 11 a.

Fig. 11 b.

Fig. 11 c.

Fig. 12.

Fig. 13 a.

Fig. 13 b.

Figs. 11-13.—Steps in the technic of administration of plasma intra-osseously.

The simplicity of the mechanism, light weight, small size, rapid utilization, and choice of two routes of administration, suggest that these units may be used with advantage by mobile groups or isolated personnel, thus, making possible the benefits of plasma to individuals at critical times under adverse conditions.*

* The same unit may be used for the emergency injection of human albumin; the containers holding 200 cc. of 25 per cent albumin solution. It has also been utilized with five grams of the sodium salt of one of the sulfa drugs in the fixed bottle B and 100 cc. of pyrogen-free water in mobile bottle A. When mixed, this results in a five per cent solution of the drug, ready for administration.

The used bottles may be taken apart, sterilized, refilled, and placed back in active service. This salvage will reduce the overall cost of a primarily inexpensive method.

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BOOK REVIEW

Blood Substitutes and Blood Transfusions. Edited by Stuart Mudd, M.D., and William Thalheimer, M.D. Charles C. Thomas. Springfield and Baltimore. 1942.

A no more timely and authoritative publication has appeared in surgical literature during this world catastrophe than the monograph on Blood Substitutes and Blood Transfusions by Mudd and Thalheimer. It is a symposium composed of the papers read before the American Human Serum Association at their meeting in 1941.

As the result of the discussion of some seventy contributors at this meeting, an early agreement was reached that the basic etiologic cause of secondary shock was a fall in the circulatory fluid volume of the blood.

Most of the program was largely devoted to such questions as procurement, preservation, administration and the relative efficiency of the various blood substitutes that have been used and recommended, both clinically and experimentally, including human hemoglobin and both human and bovine serum.

Such a group can speak authoritatively on these subjects, and the logical way in which the problem has been arranged results in an invaluable presentation which no active surgeon or hospital library can afford to omit from their shelves.

It is a remarkable contribution and both the writers and the publishers are to be congratulated.

Walter Estell Lee, M.D.

BRIEF COMMUNICATION

IMPROVED TIP FOR MILLER-ABBOTT TUBE

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The development of the Miller-Abbott tube has undoubtedly been one of the greatest advances in the management of intestinal obstruction. A great deal has been written concerning the advantages and limitations of this ingenious device.[1] It is generally conceded that the greatest handicap to the use of this method of decompressing the gastro-intestinal tract is the delay or inability of the tube to traverse the pylorus of the stomach. After the bulb portion of the tube has entered the duodenum its progress down the intestinal tract is usually rapid, and with it a rapid decompression of the small intestine.

Fig. 1.—Roentgenographic shadow of the special tip to show the arrangement of the weights, fenestra and connector.

This difficulty in getting the Miller-Abbott tube to enter the duodenum is reflected in the development of the Wilson-Sawyer modification,[2] which consisted in making the tube less flexible. Personal experience with the latter tube proved it to be a definite improvement, but the same difficulty was encountered to a lesser degree.

After experimenting with various modifications of the tip of the tube, one has been found which seems, after repeated trials, a very definite improvement in its ability to enter the duodenum promptly in cases of marked obstruction. On many occasions this tip has entered the duodenum very promptly after prolonged attempts with other tubes have proved futile. My experience with this device is submitted for further trial and evaluation.

The above mentioned special tip employs the element of weight, which is carried by gravity to the outlet of the stomach. This weight also acts to prevent the tip of the tube from coiling back toward the fundus, as often happens with the conventional tube. The weighted tip was made by incorporating lead shots into about five inches of the tip of a Levin tube. This, in turn, was connected by a short metal tube of proper caliber to the cut end of a Miller-Abbott or Wilson-Sawyer tube. Fenestra are incorporated proximal to the weights, but distal to the balloon, so that liquid and gas are removed from the intestine in advance of the tube (Fig. 1).

The technic of passing the tube is essentially that worked out by the originators of the Miller-Abbott tube. It cannot be emphasized too strongly that the successful employment of the Miller-Abbott tube necessitates constant and careful supervision by one willing to give individual attention to it. Personal experience in this respect parallels that described in other excellent articles.[3]

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